10/535414

WO 2004/046382

JC06 Rec'd PCT/PTO 19 MAY 2005.

## Product and Method

The present invention relates to oligonucleotide probes, for use in assessing gene transcript levels in a cell, which may be used in analytical techniques, particularly diagnostic techniques. Conveniently the probes are provided in kit form. Different sets of probes may be used in techniques to prepare gene expression patterns and identify, diagnose or monitor different states, such as diseases, conditions or stages thereof. Also provided are methods of identifying suitable probes and their use in methods of the invention.

The identification of quick and easy methods of sample analysis for, for example, diagnostic applications, remains the goal of many researchers. End users seek methods which are cost effective, produce statistically significant results and which may be implemented routinely without the need for highly skilled individuals.

The analysis of gene expression within cells has been used to provide information on the state of those cells and importantly the state of the individual from which the cells are derived. The relative expression of various genes in a cell has been identified as reflecting a particular state within a body. For example, cancer cells are known to exhibit altered expression of various proteins and the transcripts or the expressed proteins may therefore be used as markers of that disease state.

Thus biopsy tissue may be analysed for the presence of these markers and cells originating from the site of the disease may be identified in other tissues or fluids of the body by the presence of the markers.

Furthermore, products of the altered expression may be

10

15

20

25

30

35

released into the blood stream and these products may be analysed. In addition cells which have contacted disease cells may be affected by their direct contact with those cells resulting in altered gene expression and their expression or products of expression may be similarly analysed.

However, there are some limitations with these methods. For example, the use of specific tumour markers for identifying cancer suffers from a variety of defects, such as lack of specificity or sensitivity, association of the marker with disease states besides the specific type of cancer, and difficulty of detection in asymptomatic individuals.

In addition to the analysis of one or two marker transcripts or proteins, more recently, gene expression patterns have been analysed. Most of the work involving large-scale gene expression analysis with implications in disease diagnosis has involved clinical samples originating from diseased tissues or cells. For example, several recent publications, which demonstrate that gene expression data can be used to distinguish between similar cancer types, have used clinical samples from diseased tissues or cells (Alon et al. 1999, PNAS, 96, p6745-6750; Golub et al. 1999, Science, 286, p531-537; Alizadeh et al., 2000, Nature, 403, p503-511; Bittner et al., 2000, Nature, 406, p536-540).

However, these methods have relied on analysis of a sample containing diseased cells or products of those cells or cells which have been contacted by disease cells. Analysis of such samples relies on knowledge of the presence of a disease and its location, which may be difficult in asymptomatic patients. Furthermore, samples can not always be taken from the disease site, e.g. in diseases of the brain.

In a finding of great significance, the present inventors identified the previously untapped potential of all cells within a body to provide information

10

15

20

25

30

35

relating to the state of the organism from which the cells were derived. W098/49342 describes the analysis of the gene expression of cells distant from the site of disease, e.g. peripheral blood collected distant from a cancer site.

This finding is based on the premise that the different parts of an organism's body exist in dynamic interaction with each other. When a disease affects one part of the body, other parts of the body are also affected. The interaction results from a wide spectrum of biochemical signals that are released from the diseased area, affecting other areas in the body. Although, the nature of the biochemical and physiological changes induced by the released signals can vary in the different body parts, the changes can be measured at the level of gene expression and used for diagnostic purposes.

The physiological state of a cell in an organism is determined by the pattern with which genes are expressed in it. The pattern depends upon the internal and external biological stimuli to which said cell is exposed, and any change either in the extent or in the nature of these stimuli can lead to a change in the pattern with which the different genes are expressed in the cell. There is a growing understanding that by analysing the systemic changes in gene expression patterns in cells in biological samples, it is possible to provide information on the type and nature of the biological stimuli that are acting on them. Thus, for example, by monitoring the expression of a large number of genes in cells in a test sample, it is possible to determine whether their genes are expressed with a pattern characteristic for a particular disease, condition or stage thereof. Measuring changes in gene activities in cells, e.g. from tissue or body fluids is therefore emerging as a powerful tool for disease diagnosis.

- 4 -

Such methods have various advantages. Often, obtaining clinical samples from certain areas in the body that is diseased can be difficult and may involve undesirable invasions in the body, for example biopsy is often used to obtain samples for cancer. In some cases, such as in Alzheimer's disease the diseased brain specimen can only be obtained post-mortem. Furthermore, the tissue specimens which are obtained are often heterogeneous and may contain a mixture of both diseased and non-diseased cells, making the analysis of generated gene expression data both complex and difficult.

5

10

15

20

25

30

35

It has been suggested that a pool of tumour tissues that appear to be pathogenetically homogeneous with respect to morphological appearances of the tumour may well be highly heterogeneous at the molecular level (Alizadeh, 2000, supra), and in fact might contain tumours representing essentially different diseases (Alizadeh, 2000, supra; Golub, 1999, supra). For the purpose of identifying a disease, condition, or a stage thereof, any method that does not require clinical samples to originate directly from diseased tissues or cells is highly desirable since clinical samples representing a homogeneous mixture of cell types can be obtained from an easily accessible region in the body.

We have now identified a set of probes of surprising utility for identifying one or more diseases. Thus, we now describe probes and sets of probes derived from cells which are not disease cells and which have not contacted disease cells, which correspond to genes which exhibit altered expression in normal versus disease individuals, for use in methods of identifying, diagnosing or monitoring certain conditions, particularly diseases or stages thereof.

Thus the invention provides a set of oligonucleotide probes which correspond to genes in a cell whose expression is affected in a pattern characteristic of a particular disease, condition or

- 5 -

stage thereof, wherein said genes are systemically affected by said disease, condition or stage thereof. Preferably said genes are metabolic or house-keeping genes and preferably are constitutively moderately or highly expressed. Preferably the genes are moderately or highly expressed in the cells of the sample but not in cells from disease cells or in cells having contacted such disease cells.

5

10

15

20

25

30

35

Such probes, particularly when isolated from cells distant to the site of disease, do not rely on the development of disease to clinically recognizable levels and allow detection of a disease or condition or stage thereof very early after the onset of said disease or condition, even years before other subjective or objective symptoms appear.

As used herein "systemically" affected genes refers to genes whose expression is affected in the body without direct contact with a disease cell or disease site and the cells under investigation are not disease cells.

"Contact" as referred to herein refers to cells coming into close proximity with one another such that the direct effect of one cell on the other may be observed, e.g. an immune response, wherein these responses are not mediated by secondary molecules released from the first cell over a large distance to affect the second cell. Preferably contact refers to physical contact, or contact that is as close as is sterically possible, conveniently, cells which contact one another are found in the same unit volume, for example within 1cm<sup>3</sup>.

A "disease cell" is a cell manifesting phenotypic changes and is present at the disease site at some time during its life-span, e.g. a tumour cell at the tumour site or which has disseminated from the tumour, or a brain cell in the case of brain disorders such as Alzheimer's disease.

- 6 -

"Metabolic" or "house-keeping" genes refer to those genes responsible for expressing products involved in cell division and maintenance, e.g. non-immune function related genes.

"Moderately or highly" expressed genes refers to those present in resting cells in a copy number of more than 30-100 copies/cell (assuming an average  $3x10^5$  mRNA molecules in a cell).

Specific probes having the above described properties are provided herein.

5

10

15

20

25

30

35

Thus in one aspect, the present invention provides a set of oligonucleotide probes, wherein said set comprises at least 10 oligonucleotides selected from:

an oligonucleotide as described in Table 1 or derived from a sequence described in Table 1, or an oligonucleotide with a complementary sequence, or a functionally equivalent oligonucleotide.

"Table 1" as referred to herein refers to Table 1a and/or Table 1b. Table 1b contains reference to additional clones and sequences as disclosed herein. Similarly Tables 2 and 4 comprise 2 parts, a and b.

The invention also provides one or more oligonucleotide probes, wherein each oligonucleotide probe is selected from the oligonucleotides listed in Table 1, or derived from a sequence described in Table 1, or a complementary sequence thereof. The use of such probes in products and methods of the invention, form further aspects of the invention.

As referred to herein an "oligonucleotide" is a nucleic acid molecule having at least 6 monomers in the polymeric structure, ie. nucleotides or modified forms thereof. The nucleic acid molecule may be DNA, RNA or PNA (peptide nucleic acid) or hybrids thereof or modified versions thereof, e.g. chemically modified forms, e.g. LNA (Locked Nucleic acid), by methylation or made up of modified or non-natural bases during synthesis, providing they retain their ability to bind

- 7 -

to complementary sequences. Such oligonucleotides are used in accordance with the invention to probe target sequences and are thus referred to herein also as oligonucleotide probes or simply as probes.

5

10

15

20

25

30

An "oligonucleotide derived from a sequence described in Table 1" (or any other table) refers to a part of a sequence disclosed in that Table (e.g. Table 1-4), which satisfies the requirements of the oligonucleotide probes as described herein, e.g. in length and function. Preferably said parts have the size described hereinafter.

Preferably the oligonucleotide probes forming said set are at least 15 bases in length to allow binding of target molecules. Especially preferably said oligonucleotide probes are from 20 to 200 bases in length, e.g. from 30 to 150 bases, preferably 50-100 bases in length.

As referred to herein the term "complementary sequences" refers to sequences with consecutive complementary bases (ie. T:A, G:C) and which complementary sequences are therefore able to bind to one another through their complementarity.

Reference to "10 oligonucleotides" refers to 10 different oligonucleotides. Whilst a Table 1 oligonucleotide, a Table 1 derived oligonucleotide and their functional equivalent are considered different oligonucleotides, complementary oligonucleotides are not considered different. Preferably however, the at least 10 oligonucleotides are 10 different Table 1 oligonucleotides (or Table 1 derived oligonucleotides or their functional equivalents). Thus said 10 different oligonucleotides are preferably able to bind to 10 different transcripts.

Preferably said oligonucleotides are as described in Table 1 or are derived from a sequence described in Table 1. Especially preferably said oligonucleotides are as described in Table 2 or Table 4 or are derived

10

35

from a sequence described in either of those tables. Especially preferably the oligonucleotide (or the oligonucleotide derived therefrom) has a high occurrence as defined in Table 3, especially preferably >40%, e.g. >80 or >90, e.g. 100%.

A "set" as described refers to a collection of unique oligonucleotide probes (ie. having a distinct sequence) and preferably consists of less than 1000 oligonucleotide probes, especially less than 500 probes, e.g. preferably from 10 to 500, e.g. 10 to 100, 200 or 300, especially preferably 20 to 100, e.g. 30 to 100 probes. In some cases less than 10 probes may be used, e.g. from 2 to 9 probes, e.g. 5 to 9 probes.

It will be appreciated that increasing the number of probes will prevent the possibility of poor analysis, 15 e.g. misdiagnosis by comparison to other diseases which could similarly alter the expression of the particular genes in question. Other oligonucleotide probes not described herein may also be present, particularly if they aid the ultimate use of the set of oligonucleotide 20 probes. However, preferably said set consists only of said Table 1 oligonucleotides, Table 1 derived oligonucleotides, complementary sequences or functionally equivalent oligonucleotides, or a sub-set 25 thereof (e.g. of the size as described above), preferably a sub-set for which sequences are provided herein (see Table 1 and its footnote). Especially preferably said set consists only of said Table 1 oligonucleotides, Table 1 derived oligonucleotides, or complementary sequences thereof, or a sub-set thereof. 30

Multiple copies of each unique oligonucleotide probe, e.g. 10 or more copies, may be present in each set, but constitute only a single probe.

A set of oligonucleotide probes, which may preferably be immobilized on a solid support or have means for such immobilization, comprises the at least 10 oligonucleotide probes selected from those described

- 9 -

hereinbefore. Especially preferably said probes are selected from those having high occurrence as described in Table 3 and as mentioned above. As mentioned above, these 10 probes must be unique and have different sequences. Having said this however, two separate probes may be used which recognize the same gene but reflect different splicing events. However oligonucleotide probes which are complementary to, and bind to distinct genes are preferred.

5

30

35

As described herein a "functionally equivalent" 10 oligonucleotide to those described in Table 1 or derived therefrom refers to an oligonucleotide which is capable of identifying the same gene as an oligonucleotide of Table 1 or derived therefrom, ie. it can bind to the 15 same mRNA molecule (or DNA) transcribed from a gene (target nucleic acid molecule) as the Table 1 oligonucleotide or the Table 1 derived oligonucleotide (or its complementary sequence). Preferably said functionally equivalent oligonucleotide is capable of recognizing, ie. binding to the same splicing product as 20 a Table 1 oligonucleotide or a Table 1 derived oligonucleotide. Preferably said mRNA molecule is the full length mRNA molecule which corresponds to the Table 1 oligonucleotide or the Table 1 derived 25 oligonucleotide.

As referred to herein "capable of binding" or "binding" refers to the ability to hybridize under conditions described hereinafter.

Alternatively expressed, functionally equivalent oligonucleotides (or complementary sequences) have sequence identity or will hybridize, as described hereinafter, to a region of the target molecule to which molecule a Table 1 oligonucleotide or a Table 1 derived oligonucleotide or a complementary oligonucleotide binds. Preferably, functionally equivalent oligonucleotides (or their complementary sequences) hybridize to one of the mRNA sequences which corresponds

to a Table 1 oligonucleotide or a Table 1 derived oligonucleotide under the conditions described hereinafter or has sequence identity to a part of one of the mRNA sequences which corresponds to a Table 1 oligonucleotide or a Table 1 derived oligonucleotide. A "part" in this context refers to a stretch of at least 5, e.g. at least 10 or 20 bases, such as from 5 to 100, e.g. 10 to 50 or 15 to 30 bases.

In a particularly preferred aspect, the functionally equivalent oligonucleotide binds to all or 10 a part of the region of a target nucleic acid molecule (mRNA or cDNA) to which the Table 1 oligonucleotide or Table 1 derived oligonucleotide binds. A "target" nucleic acid molecule is the gene transcript or related 15 product e.g. mRNA, or cDNA, or amplified product thereof. Said "region" of said target molecule to which said Table 1 oligonucleotide or Table 1 derived oligonucleotide binds is the stretch over which complementarity exists. At its largest this region is the whole length of the Table 1 oligonucleotide or Table 20 1 derived oligonucleotide, but may be shorter if the entire Table 1 sequence or Table 1 derived oligonucleotide is not complementary to a region of the target sequence.

Preferably said part of said region of said target molecule is a stretch of at least 5, e.g. at least 10 or 20 bases, such as from 5 to 100, e.g. 10 to 50 or 15 to 30 bases. This may for example be achieved by said functionally equivalent oligonucleotide having several identical bases to the bases of the Table 1 oligonucleotide or the Table 1 derived oligonucleotide. These bases may be identical over consecutive stretches, e.g. in a part of the functionally equivalent oligonucleotide, or may be present non-consecutively, but provide sufficient complementarity to allow binding to the target sequence.

Thus in a preferred feature, said functionally

- 11 -

equivalent oligonucleotide hybridizes under conditions of high stringency to a Table 1 oligonucleotide or a Table 1 derived oligonucleotide or the complementary sequence thereof. Alternatively expressed, said functionally equivalent oligonucleotide exhibits high 5 sequence identity to all or part of a Table 1 oligonucleotide. Preferably said functionally equivalent oligonucleotide has at least 70% sequence identity, preferably at least 80%, e.g. at least 90, 95, 98 or 99%, to all of a Table 1 oligonucleotide or a part 10 thereof. As used in this context, a "part" refers to a stretch of at least 5, e.g. at least 10 or 20 bases, such as from 5 to 100, e.g. 10 to 50 or 15 to 30 bases, in said Table 1 oligonucleotide. Especially preferably when sequence identity to only a part of said Table 1 15 oligonucleotide is present, the sequence identity is high, e.g. at least 80% as described above.

Functionally equivalent oligonucleotides which satisfy the above stated functional requirements include those which are derived from the Table 1 oligonucleotides and also those which have been modified by single or multiple nucleotide base (or equivalent) substitution, addition and/or deletion, but which nonetheless retain functional activity, e.g. bind to the same target molecule as the Table 1 oligonucleotide or the Table 1 derived oligonucleotide from which they are further derived or modified. Preferably said modification is of from 1 to 50, e.g. from 10 to 30, preferably from 1 to 5 bases. Especially preferably only minor modifications are present, e.g. variations in less than 10 bases, e.g. less than 5 base changes.

20

25

30

35

Within the meaning of "addition" equivalents are included oligonucleotides containing additional sequences which are complementary to the consecutive stretch of bases on the target molecule to which the Table 1 oligonucleotide or the Table 1 derived oligonucleotide binds. Alternatively the addition may

10

25

comprise a different, unrelated sequence, which may for example confer a further property, e.g. to provide a means for immobilization such as a linker to bind the oligonucleotide probe to a solid support.

Particularly preferred are naturally occurring equivalents such as biological variants, e.g. allelic, geographical or allotypic variants, e.g. oligonucleotides which correspond to a genetic variant, for example as present in a different species.

Functional equivalents include oligonucleotides with modified bases, e.g. using non-naturally occurring bases. Such derivatives may be prepared during synthesis or by post production modification.

"Hybridizing" sequences which bind under conditions
of low stringency are those which bind under nonstringent conditions (for example, 6x SSC/50% formamide
at room temperature) and remain bound when washed under
conditions of low stringency (2 X SSC, room temperature,
more preferably 2 X SSC, 42°C). Hybridizing under high
stringency refers to the above conditions in which
washing is performed at 2 X SSC, 65°C (where SSC = 0.15M
NaCl, 0.015M sodium citrate, pH 7.2).

"Sequence identity" as referred to herein refers to the value obtained when assessed using ClustalW (Thompson et al., 1994, Nucl. Acids Res., 22, p4673-4680) with the following parameters:

Pairwise alignment parameters - Method: accurate, Matrix: IUB, Gap open penalty: 15.00, Gap extension penalty: 6.66;

Multiple alignment parameters - Matrix: IUB, Gap open penalty: 15.00, % identity for delay: 30, Negative matrix: no, Gap extension penalty: 6.66, DNA transitions weighting: 0.5.

Sequence identity at a particular base is intended to include identical bases which have simply been derivatized.

The invention also extends to polypeptides encoded

- 13 -

by the mRNA sequence to which a Table 1 oligonucleotide or a Table 1 derived oligonucleotide binds. The invention further extends to antibodies which bind to any of said polypeptides.

5

10

15

20

25

30

As described above, conveniently said set of oligonucleotide probes may be immobilized on one or more solid supports. Single or preferably multiple copies of each unique probe are attached to said solid supports, e.g. 10 or more, e.g. at least 100 copies of each unique probe are present.

One or more unique oligonucleotide probes may be associated with separate solid supports which together form a set of probes immobilized on multiple solid support, e.g. one or more unique probes may be immobilized on multiple beads, membranes, filters, biochips etc. which together form a set of probes, which together form modules of the kit described hereinafter. The solid support of the different modules are conveniently physically associated although the signals associated with each probe (generated as described hereinafter) must be separately determinable.

Alternatively, the probes may be immobilized on discrete portions of the same solid support, e.g. each unique oligonucleotide probe, e.g. in multiple copies, may be immobilized to a distinct and discrete portion or region of a single filter or membrane, e.g. to generate an array.

A combination of such techniques may also be used, e.g. several solid supports may be used which each immobilize several unique probes.

The expression "solid support" shall mean any solid material able to bind oligonucleotides by hydrophobic, ionic or covalent bridges.

"Immobilization" as used herein refers to

reversible or irreversible association of the probes to
said solid support by virtue of such binding. If
reversible, the probes remain associated with the solid

support for a time sufficient for methods of the invention to be carried out.

5

10

15

20

25

30

35

Numerous solid supports suitable as immobilizing moieties according to the invention, are well known in the art and widely described in the literature and generally speaking, the solid support may be any of the well-known supports or matrices which are currently widely used or proposed for immobilization, separation etc. in chemical or biochemical procedures. materials include, but are not limited to, any synthetic organic polymer such as polystyrene, polyvinylchloride, polyethylene; or nitrocellulose and cellulose acetate; or tosyl activated surfaces; or glass or nylon or any surface carrying a group suited for covalent coupling of nucleic acids. The immobilizing moieties may take the form of particles, sheets, gels, filters, membranes, microfibre strips, tubes or plates, fibres or capillaries, made for example of a polymeric material e.g. agarose, cellulose, alginate, teflon, latex or polystyrene or magnetic beads. Solid supports allowing the presentation of an array, preferably in a single dimension are preferred, e.g. sheets, filters, membranes, plates or biochips.

Attachment of the nucleic acid molecules to the solid support may be performed directly or indirectly. For example if a filter is used, attachment may be performed by UV-induced crosslinking. Alternatively, attachment may be performed indirectly by the use of an attachment moiety carried on the oligonucleotide probes and/or solid support. Thus for example, a pair of affinity binding partners may be used, such as avidin, streptavidin or biotin, DNA or DNA binding protein (e.g. either the lac I repressor protein or the lac operator sequence to which it binds), antibodies (which may be mono- or polyclonal), antibody fragments or the epitopes or haptens of antibodies. In these cases, one partner of the binding pair is attached to (or is inherently

part of) the solid support and the other partner is attached to (or is inherently part of) the nucleic acid molecules.

As used herein an "affinity binding pair" refers to two components which recognize and bind to one another specifically (ie. in preference to binding to other molecules). Such binding pairs when bound together form a complex.

5

10

15

20

25

30

Attachment of appropriate functional groups to the solid support may be performed by methods well known in the art, which include for example, attachment through hydroxyl, carboxyl, aldehyde or amino groups which may be provided by treating the solid support to provide suitable surface coatings. Solid supports presenting appropriate moieties for attachment of the binding partner may be produced by routine methods known in the art.

Attachment of appropriate functional groups to the oligonucleotide probes of the invention may be performed by ligation or introduced during synthesis or amplification, for example using primers carrying an appropriate moiety, such as biotin or a particular sequence for capture.

Conveniently, the set of probes described hereinbefore is provided in kit form.

Thus viewed from a further aspect the present invention provides a kit comprising a set of oligonucleotide probes as described hereinbefore immobilized on one or more solid supports.

Preferably, said probes are immobilized on a single solid support and each unique probe is attached to a different region of said solid support. However, when attached to multiple solid supports, said multiple solid supports form the modules which make up the kit.

Especially preferably said solid support is a sheet, filter, membrane, plate or biochip.

Optionally the kit may also contain information

10

15

20

25

30

relating to the signals generated by normal or diseased samples (as discussed in more detail hereinafter in relation to the use of the kits), standardizing materials, e.g. mRNA or cDNA from normal and/or diseased samples for comparative purposes, labels for incorporation into cDNA, adapters for introducing nucleic acid sequences for amplification purposes, primers for amplification and/or appropriate enzymes, buffers and solutions. Optionally said kit may also contain a package insert describing how the method of the invention should be performed, optionally providing standard graphs, data or software for interpretation of results obtained when performing the invention.

The use of such kits to prepare a standard diagnostic gene transcript pattern as described hereinafter forms a further aspect of the invention.

The set of probes as described herein have various uses. Principally however they are used to assess the gene expression state of a test cell to provide information relating to the organism from which said cell is derived. Thus the probes are useful in diagnosing, identifying or monitoring a disease or condition or stage thereof in an organism.

Thus in a further aspect the invention provides the use of a set of oligonucleotide probes or a kit as described hereinbefore to determine the gene expression pattern of a cell which pattern reflects the level of gene expression of genes to which said oligonucleotide probes bind, comprising at least the steps of:

- a) isolating mRNA from said cell, which may optionally be reverse transcribed to cDNA;
- b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotide probes or a kit as defined herein; and
- c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce said pattern.

The mRNA and cDNA as referred to in this method,

- 17 -

and the methods hereinafter, encompass derivatives or copies of said molecules, e.g. copies of such molecules such as those produced by amplification or the preparation of complementary strands, but which retain the identity of the mRNA sequence, ie. would hybridize to the direct transcript (or its complementary sequence) by virtue of precise complementarity, or sequence identity, over at least a region of said molecule. Ιt will be appreciated that complementarity will not exist over the entire region where techniques have been used which may truncate the transcript or introduce new sequences, e.g. by primer amplification. convenience, said mRNA or cDNA is preferably amplified prior to step b). As with the oligonucleotides described herein said molecules may be modified, e.g. by using non-natural bases during synthesis providing complementarity remains. Such molecules may also carry additional moieties such as signalling or immobilizing means.

5

10

15

20

25

30

35

The various steps involved in the method of preparing such a pattern are described in more detail hereinafter.

As used herein "gene expression" refers to transcription of a particular gene to produce a specific mRNA product (ie. a particular splicing product). The level of gene expression may be determined by assessing the level of transcribed mRNA molecules or cDNA molecules reverse transcribed from the mRNA molecules or products derived from those molecules, e.g. by amplification.

The "pattern" created by this technique refers to information which, for example, may be represented in tabular or graphical form and conveys information about the signal associated with two or more oligonucleotides. Preferably said pattern is expressed as an array of numbers relating to the expression level associated with each probe.

10

15

20

25

30

35

Preferably, said pattern is established using the following linear model:

y = Xb + f

wherein, X is the matrix of gene expression data and y
is the response variable, b is the regression
coefficient vector and f the estimated residual vector.
Although many different methods can be used to establish
the relationship provided in equation 1, especially
preferably the partial Least Squares Regression (PLSR)
method is used for establishing the relationship in
equation 1.

The probes are thus used to generate a pattern which reflects the gene expression of a cell at the time of its isolation. The pattern of expression is characteristic of the circumstances under which that cells finds itself and depends on the influences to which the cell has been exposed. Thus, a characteristic gene transcript pattern standard or fingerprint (standard probe pattern) for cells from an individual with a particular disease or condition may be prepared and used for comparison to transcript patterns of test cells. This has clear applications in diagnosing, monitoring or identifying whether an organism is suffering from a particular disease, condition or stage thereof.

The standard pattern is prepared by determining the extent of binding of total mRNA (or cDNA or related product), from cells from a sample of one or more organisms with the disease or condition or stage thereof, to the probes. This reflects the level of transcripts which are present which correspond to each unique probe. The amount of nucleic acid material which binds to the different probes is assessed and this information together forms the gene transcript pattern standard of that disease or condition or stage thereof. Each such standard pattern is characteristic of the disease, condition or stage thereof.

- 19 -

In a further aspect therefore, the present invention provides a method of preparing a standard gene transcript pattern characteristic of a disease or condition or stage thereof in an organism comprising at least the steps of:

- a) isolating mRNA from the cells of a sample of one or more organisms having the disease or condition or stage thereof, which may optionally be reverse transcribed to cDNA;
- b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotides or a kit as described hereinbefore specific for said disease or condition or stage thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and

5

20

25

30

35

c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce a characteristic pattern reflecting the level of gene expression of genes to which said oligonucleotides bind, in the sample with the disease, condition or stage thereof.

For convenience, said oligonucleotides are preferably immobilized on one or more solid supports.

The standard pattern for a great number of diseases or conditions and different stages thereof using particular probes may be accumulated in databases and be made available to laboratories on request.

"Disease" samples and organisms as referred to herein refer to organisms (or samples from the same) with an underlying pathological disturbance relative to a normal organism (or sample), in a symptomatic or asymptomatic organism, which may result, for example, from infection or an acquired or congenital genetic imperfection. Such organisms are known to have, or which exhibit, the disease or condition or stage thereof under study.

A "condition" refers to a state of the mind or body of an organism which has not occurred through disease,

10

15

35

e.g. the presence of an agent in the body such as a toxin, drug or pollutant, or pregnancy.

"Stages" thereof refer to different stages of the disease or condition which may or may not exhibit particular physiological or metabolic changes, but do exhibit changes at the genetic level which may be detected as altered gene expression. It will be appreciated that during the course of a disease or condition the expression of different transcripts may Thus at different stages, altered expression may not be exhibited for particular transcripts compared to "normal" samples. However, combining information from several transcripts which exhibit altered expression at one or more stages through the course of the disease or condition can be used to provide a characteristic pattern which is indicative of a particular stage of the disease or condition. Thus for example different stages in cancer, e.g. pre-stage I, stage I, stage II, II or IV can be identified.

"Normal" as used herein refers to organisms or samples which are used for comparative purposes.

Preferably, these are "normal" in the sense that they do not exhibit any indication of, or are not believed to have, any disease or condition that would affect gene expression, particularly in respect of the disease for which they are to be used as the normal standard. However, it will be appreciated that different stages of a disease or condition may be compared and in such cases, the "normal" sample may correspond to the earlier stage of the disease or condition.

As used herein a "sample" refers to any material obtained from the organism, e.g. human or non-human animal under investigation which contains cells and includes, tissues, body fluid or body waste or in the case of prokaryotic organisms, the organism itself. "Body fluids" include blood, saliva, spinal fluid, semen, lymph. "Body waste" includes urine, expectorated

5

10

15

20

25

30

35

- 21 -

matter (pulmonary patients), faeces etc. "Tissue samples" include tissue obtained by biopsy, by surgical interventions or by other means e.g. placenta. Preferably however, the samples which are examined are from areas of the body not apparently affected by the disease or condition. The cells in such samples are not disease cells, e.g. cancer cells, have not been in contact with such disease cells and do not originate from the site of the disease or condition. The "site of disease" is considered to be that area of the body which manifests the disease in a way which may be objectively determined, e.g. a tumour or area of inflammation. for example peripheral blood may be used for the diagnosis of non-haematopoietic cancers, and the blood does not require the presence of malignant or disseminated cells from the cancer in the blood. Similarly in diseases of the brain, in which no diseased cells are found in the blood due to the blood:brain barrier, peripheral blood may still be used in the methods of the invention.

It will however be appreciated that the method of preparing the standard transcription pattern and other methods of the invention are also applicable for use on living parts of eukaryotic organisms such as cell lines and organ cultures and explants.

As used herein, reference to "corresponding" sample etc. refers to cells preferably from the same tissue, body fluid or body waste, but also includes cells from tissue, body fluid or body waste which are sufficiently similar for the purposes of preparing the standard or test pattern. When used in reference to genes "corresponding" to the probes, this refers to genes which are related by sequence (which may be complementary) to the probes although the probes may reflect different splicing products of expression.

"Assessing" as used herein refers to both quantitative and qualitative assessment which may be

- 22 -

determined in absolute or relative terms.

5

10

15

20

25

30

35

The invention may be put into practice as follows. To prepare a standard transcript pattern for a particular disease, condition or stage thereof, sample mRNA is extracted from the cells of tissues, body fluid or body waste according to known techniques (see for example Sambrook et. al. (1989), Molecular Cloning: A laboratory manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.) from a diseased individual or organism.

Owing to the difficulties in working with RNA, the RNA is preferably reverse transcribed at this stage to form first strand cDNA. Cloning of the cDNA or selection from, or using, a cDNA library is not however necessary in this or other methods of the invention. Preferably, the complementary strands of the first strand cDNAs are synthesized, ie. second strand cDNAs, but this will depend on which relative strands are present in the oligonucleotide probes. The RNA may however alternatively be used directly without reverse transcription and may be labelled if so required.

Preferably the cDNA strands are amplified by known amplification techniques such as the polymerase chain reaction (PCR) by the use of appropriate primers. Alternatively, the cDNA strands may be cloned with a vector, used to transform a bacteria such as E. coli which may then be grown to multiply the nucleic acid molecules. When the sequence of the cDNAs are not known, primers may be directed to regions of the nucleic acid molecules which have been introduced. Thus for example, adapters may be ligated to the cDNA molecules and primers directed to these portions for amplification of the cDNA molecules. Alternatively, in the case of eukaryotic samples, advantage may be taken of the polyA tail and cap of the RNA to prepare appropriate primers.

To produce the standard diagnostic gene transcript pattern or fingerprint for a particular disease or

- 23 -

condition or stage thereof, the above described oligonucleotide probes are used to probe mRNA or cDNA of the diseased sample to produce a signal for hybridization to each particular oligonucleotide probe species, ie. each unique probe. A standard control gene transcript pattern may also be prepared if desired using mRNA or cDNA from a normal sample. Thus, mRNA or cDNA is brought into contact with the oligonucleotide probe under appropriate conditions to allow hybridization.

5

10

15

20

25

30

35

When multiple samples are probed, this may be performed consecutively using the same probes, e.g. on one or more solid supports, ie. on probe kit modules, or by simultaneously hybridizing to corresponding probes, e.g. the modules of a corresponding probe kit.

To identify when hybridization occurs and obtain an indication of the number of transcripts/cDNA molecules which become bound to the oligonucleotide probes, it is necessary to identify a signal produced when the transcripts (or related molecules) hybridize (e.g. by detection of double stranded nucleic acid molecules or detection of the number of molecules which become bound, after removing unbound molecules, e.g. by washing).

In order to achieve a signal, either or both components which hybridize (ie. the probe and the transcript) carry or form a signalling means or a part This "signalling means" is any moiety capable thereof. of direct or indirect detection by the generation or presence of a signal. The signal may be any detectable physical characteristic such as conferred by radiation emission, scattering or absorption properties, magnetic properties, or other physical properties such as charge, size or binding properties of existing molecules (e.g. labels) or molecules which may be generated (e.g. gas emission etc.). Techniques are preferred which allow signal amplification, e.g. which produce multiple signal events from a single active binding site, e.g. by the catalytic action of enzymes to produce multiple

- 24 -

detectable products.

5

30

Conveniently the signalling means may be a label which itself provides a detectable signal. Conveniently this may be achieved by the use of a radioactive or other label which may be incorporated during cDNA production, the preparation of complementary cDNA strands, during amplification of the target mRNA/cDNA or added directly to target nucleic acid molecules.

Appropriate labels are those which directly or indirectly allow detection or measurement of the 10 presence of the transcripts/cDNA. Such labels include for example radiolabels, chemical labels, for example chromophores or fluorophores (e.g. dyes such as fluorescein and rhodamine), or reagents of high electron density such as ferritin, haemocyanin or colloidal gold. 15 Alternatively, the label may be an enzyme, for example peroxidase or alkaline phosphatase, wherein the presence of the enzyme is visualized by its interaction with a suitable entity, for example a substrate. The label may also form part of a signalling pair wherein the other 20 member of the pair is found on, or in close proximity to, the oligonucleotide probe to which the transcript/cDNA binds, for example, a fluorescent compound and a quench fluorescent substrate may be used. A label may also be provided on a different entity, such 25 as an antibody, which recognizes a peptide moiety attached to the transcripts/cDNA, for example attached to a base used during synthesis or amplification.

A signal may be achieved by the introduction of a label before, during or after the hybridization step. Alternatively, the presence of hybridizing transcripts may be identified by other physical properties, such as their absorbance, and in which case the signalling means is the complex itself.

The amount of signal associated with each oligonucleotide probe is then assessed. The assessment may be quantitative or qualitative and may be based on

- 25 -

binding of a single transcript species (or related cDNA or other products) to each probe, or binding of multiple transcript species to multiple copies of each unique probe. It will be appreciated that quantitative results will provide further information for the transcript fingerprint of the disease which is compiled. This data may be expressed as absolute values (in the case of macroarrays) or may be determined relative to a particular standard or reference e.g. a normal control sample.

5

10

15

20

25

30

35

Furthermore it will be appreciated that the standard diagnostic gene pattern transcript may be prepared using one or more disease samples (and normal samples if used) to perform the hybridization step to obtain patterns not biased towards a particular individual's variations in gene expression.

The use of the probes to prepare standard patterns and the standard diagnostic gene transcript patterns thus produced for the purpose of identification or diagnosis or monitoring of a particular disease or condition or stage thereof in a particular organism forms a further aspect of the invention.

Once a standard diagnostic fingerprint or pattern has been determined for a particular disease or condition using the selected oligonucleotide probes, this information can be used to identify the presence, absence or extent or stage of that disease or condition in a different test organism or individual.

To examine the gene expression pattern of a test sample, a test sample of tissue, body fluid or body waste containing cells, corresponding to the sample used for the preparation of the standard pattern, is obtained from a patient or the organism to be studied. A test gene transcript pattern is then prepared as described hereinbefore as for the standard pattern.

In a further aspect therefore, the present invention provides a method of preparing a test gene

- 26 -

transcript pattern comprising at least the steps of:

a) isolating mRNA from the cells of a sample of said test organism, which may optionally be reverse transcribed to cDNA;

5

10

15

20

25

30

35

- b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotides or a kit as described hereinbefore specific for a disease or condition or stage thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and
- c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce said pattern reflecting the level of gene expression of genes to which said oligonucleotides bind, in said test sample.

This test pattern may then be compared to one or more standard patterns to assess whether the sample contains cells having the disease, condition or stage thereof.

Thus viewed from a further aspect the present invention provides a method of diagnosing or identifying or monitoring a disease or condition or stage thereof in an organism, comprising the steps of:

- a) isolating mRNA from the cells of a sample of said organism, which may optionally be reverse transcribed to cDNA;
- b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotides or a kit as described hereinbefore specific for said disease or condition or stage thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation;
- c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce a characteristic pattern reflecting the level of gene expression of genes to which said oligonucleotides bind, in said sample; and
- d) comparing said pattern to a standard

- 27 -

diagnostic pattern prepared according to the method of the invention using a sample from an organism corresponding to the organism and sample under investigation to determine the presence of said disease or condition or a stage thereof in the organism under investigation.

The method up to and including step c) is the preparation of a test pattern as described above.

5

10

15

20

25

30

35

As referred to herein, "diagnosis" refers to determination of the presence or existence of a disease or condition or stage thereof in an organism.

"Monitoring" refers to establishing the extent of a disease or condition, particularly when an individual is known to be suffering from a disease or condition, for example to monitor the effects of treatment or the development of a disease or condition, e.g. to determine the suitability of a treatment or provide a prognosis.

The presence of the disease or condition or stage thereof may be determined by determining the degree of correlation between the standard and test samples' This necessarily takes into account the range of values which are obtained for normal and diseased samples. Although this can be established by obtaining standard deviations for several representative samples binding to the probes to develop the standard, it will be appreciated that single samples may be sufficient to generate the standard pattern to identify a disease if the test sample exhibits close enough correlation to that standard. Conveniently, the presence, absence, or extent of a disease or condition or stage thereof in a test sample can be predicted by inserting the data relating to the expression level of informative probes in test sample into the standard diagnostic probe pattern established according to equation 1.

Data generated using the above mentioned methods may be analysed using various techniques from the most

10

15

20

25

30

35

basic visual representation (e.g. relating to intensity) to more complex data manipulation to identify underlying patterns which reflect the interrelationship of the level of expression of each gene to which the various probes bind, which may be quantified and expressed mathematically. Conveniently, the raw data thus generated may be manipulated by the data processing and statistical methods described hereinafter, particularly normalizing and standardizing the data and fitting the data to a classification model to determine whether said test data reflects the pattern of a particular disease, condition or stage thereof.

The methods described herein may be used to identify, monitor or diagnose a disease, condition or ailment or its stage or progression, for which the oligonucleotide probes are informative. "Informative" probes as described herein, are those which reflect genes which have altered expression in the diseases or conditions in question, or particular stages thereof. Probes of the invention may not be sufficiently informative for diagnostic purposes when used alone, but are informative when used as one of several probes to provide a characteristic pattern, e.g. in a set as described hereinbefore.

Preferably said probes correspond to genes which are systemically affected by said disease, condition or stage thereof. Especially preferably said genes, from which transcripts are derived which bind to probes of the invention, are metabolic or house-keeping genes and preferably are moderately or highly expressed. The advantage of using probes directed to moderately or highly expressed genes is that smaller clinical samples are required for generating the necessary gene expression data set, e.g. less than 1ml blood samples.

Furthermore, it has been found that such genes which are already being actively transcribed tend to be more prone to being influenced, in a positive or

- 29 -

negative way, by new stimuli. In addition, since transcripts are already being produced at levels which are generally detectable, small changes in those levels are readily detectable as for example, a certain detectable threshold does not need to be reached.

5

10

15

20

.25

30

35

In preferred methods of the invention, the set of probes of the invention are informative for a variety of different diseases, conditions or stages thereof. A sub-set of the probes disclosed herein may be used for diagnosis, identification or monitoring a particular disease, condition or stage thereof.

Thus the probes may be used to diagnose or identify or monitor any condition, ailment, disease or reaction that leads to the relative increase or decrease in the activity of informative genes of any or all eukaryotic or prokaryotic organisms regardless of whether these changes have been caused by the influence of bacteria, virus, prions, parasites, fungi, radiation, natural or artificial toxins, drugs or allergens, including mental conditions due to stress, neurosis, psychosis or deteriorations due to the ageing of the organism, and conditions or diseases of unknown cause, providing a sub-set of the probes as described herein are informative for said disease or condition or stage thereof.

Such diseases include those which result in metabolic or physiological changes, such as feverassociated diseases such as influenza or malaria. Other diseases which may be detected include for example yellow fever, sexually transmitted diseases such as gonorrhea, fibromyalgia, candida-related complex, cancer (for example of the stomach, lung, breast, prostate gland, bowel, skin, colon, ovary etc), Alzheimer's disease, disease caused by retroviruses such as HIV, senile dementia, multiple sclerosis and Creutzfeldt-Jakob disease to mention a few

The invention may also be used to identify patients

- 30 -

with psychiatric or psychosomatic diseases such as schizophrenia and eating disorders. Of particular importance is the use of this method to detect diseases, conditions, or stages thereof, which are not readily detectable by known diagnostic methods, such as HIV which is generally not detectable using known techniques 1 to 4 months following infection. Conditions which may be identified include for example drug abuse, such as the use of narcotics, alcohol, steroids or performance enhancing drugs.

5

10

15

20

25

30

35

Preferably said disease to be identified or monitored is a cancer or a degenerative brain disorder (such as Alzheimer's or Parkinson's disease).

In particular, a set of oligonucleotide probes, wherein said set comprises at least 10 oligonucleotides selected from:

an oligonucleotide as described in Table 4 or an oligonucleotide derived therefrom or an oligonucleotide with a complementary sequence, or a functionally equivalent oligonucleotide, may be used for diagnosis or identification or monitoring the progression of Alzheimer's disease. Similarly Table 2 probes and Table 2 derived probes and their functional equivalents may be used to diagnose, identify or monitor the progression of breast cancer. Especially preferably the probes used for breast cancer analysis are selected based on their occurrence as set forth in Table 3 and as described hereinbefore.

The diagnostic method may be used alone as an alternative to other diagnostic techniques or in addition to such techniques. For example, methods of the invention may be used as an alternative or additive diagnostic measure to diagnosis using imaging techniques such as Magnetic Resonance Imagine (MRI), ultrasound imaging, nuclear imaging or X-ray imaging, for example in the identification and/or diagnosis of tumours.

The methods of the invention may be performed on

5

10

15

20

25

. 30

35

- 31 -

cells from prokaryotic or eukaryotic organisms which may be any eukaryotic organisms such as human beings, other mammals and animals, birds, insects, fish and plants, and any prokaryotic organism such as a bacteria.

Preferred non-human animals on which the methods of the invention may be conducted include, but are not limited to mammals, particularly primates, domestic animals, livestock and laboratory animals. Thus preferred animals for diagnosis include mice, rats, guinea pigs, cats, dogs, pigs, cows, goats, sheep, horses. Particularly preferably the disease state or condition of humans is diagnosed, identified or monitored.

As described above, the sample under study may be any convenient sample which may be obtained from an organism. Preferably however, as mentioned above, the sample is obtained from a site distant to the site of disease and the cells in such samples are not disease cells, have not been in contact with such cells and do not originate from the site of the disease or condition. In such cases, although preferably absent, the sample may contain cells which do not fulfil these criteria. However, since the probes of the invention are concerned with transcripts whose expression is altered in cells which do satisfy these criteria, the probes are specifically directed to detecting changes in transcript levels in those cells even if in the presence of other, background cells.

It has been found that the cells from such samples show significant and informative variations in the gene expression of a large number of genes. Thus, the same probe (or several probes) may be found to be informative in determinations regarding two or more diseases, conditions or stages thereof by virtue of the particular level of transcripts binding to that probe or the interrelationship of the extent of binding to that probe relative to other probes. As a consequence, it is

20

25

30

35

possible to use a relatively small number of probes for screening for multiple disorders or diseases. This has consequences with regard to the selection of probes, discussed in relation to random identification of probes hereinafter, but also for the use of a single set of probes for more than one diagnosis. Table 9 which represents preferred probes of the invention discloses probes which are informative for both Alzheimer's and breast cancer.

Thus, the present invention also provides sets of probes for diagnosing, identifying or monitoring two or more diseases, conditions or stages thereof, wherein at least one of said probes is suitable for said diagnosing, identifying or monitoring at least two of said diseases, conditions or stages thereof, and kits and methods of using the same. Preferably at least 5 probes, e.g. from 5 to 15 probes, are used in at least two diagnoses.

Thus, in a further preferred aspect, the present invention provides a method of diagnosis or identification or monitoring as described hereinbefore for the diagnosis, identification or monitoring of two or more diseases, conditions or stages thereof in an organism, wherein said test pattern produced in step c) of the diagnostic method is compared in step d) to at least two standard diagnostic patterns prepared as described previously, wherein each standard diagnostic pattern is a pattern generated for a different disease or condition or stage thereof.

Whilst in a preferred aspect the methods of assessment concern the development of a gene transcript pattern from a test sample and comparison of the same to a standard pattern, the elevation or depression of expression of certain markers may also be examined by examining the products of expression and the level of those products. Thus a standard pattern in relation to the expressed product may be generated.

- 33 -

In such methods the levels of expression of a set of polypeptides encoded by the gene to which an oligonucleotide of Table 1 or a Table 1 derived oligonucleotide, binds, are analysed.

5

10

15

20

25

30

35

Various diagnostic methods may be used to assess the amount of polypeptides (or fragments thereof) which are present. The presence or concentration of polypeptides may be examined, for example by the use of a binding partner to said polypeptide (e.g. an antibody), which may be immobilized, to separate said polypeptide from the sample and the amount of polypeptide may then be determined.

"Fragments" of the polypeptides refers to a domain or region of said polypeptide, e.g. an antigenic fragment, which is recognizable as being derived from said polypeptide to allow binding of a specific binding partner. Preferably such a fragment comprises a significant portion of said polypeptide and corresponds to a product of normal post-synthesis processing.

Thus in a further aspect the present invention provides a method of preparing a standard gene transcript pattern characteristic of a disease or condition or stage thereof in an organism comprising at least the steps of:

a) releasing target polypeptides from a sample of one or more organisms having the disease or condition or stage thereof;

b) contacting said target polypeptides with one or more binding partners, wherein each binding partner is specific to a marker polypeptide (or a fragment thereof) encoded by the gene to which an oligonucleotide of Table 1 (or derived from a sequence described in Table 1) binds, to allow binding of said binding partners to said target polypeptides, wherein said marker polypeptides are specific for said disease or condition thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and

- 34 -

c) assessing the target polypeptide binding to said binding partners to produce a characteristic pattern reflecting the level of gene expression of genes which express said marker polypeptides, in the sample with the disease, condition or stage thereof.

5

10

35

As used herein "target polypeptides" refer to those polypeptides present in a sample which are to be detected and "marker polypeptides" are polypeptides which are encoded by the genes to which Table 1 oligonucleotides or Table 1 derived oligonucleotides bind. The target and marker polypeptides are identical or at least have areas of high similarity, e.g. epitopic regions to allow recognition and binding of the binding partner.

"Release" of the target polypeptides refers to 15 appropriate treatment of a sample to provide the polypeptides in a form accessible for binding of the binding partners, e.g. by lysis of cells where these are The samples used in this case need not present. necessarily comprise cells as the target polypeptides 20 may be released from cells into the surrounding tissue or fluid, and this tissue or fluid may be analysed, e.g. urine or blood. Preferably however the preferred samples as described herein are used. "Binding partners" comprise the separate entities which together 25 make an affinity binding pair as described above, wherein one partner of the binding pair is the target or marker polypeptide and the other partner binds specifically to that polypeptide, e.g. an antibody. 30

Various arrangements may be envisaged for detecting the amount of binding pairs which form. In its simplest form, a sandwich type assay e.g. an immunoassay such as an ELISA, may be used in which an antibody specific to the polypeptide and carrying a label (as described elsewhere herein) may be bound to the binding pair (e.g. the first antibody:polypeptide pair) and the amount of label detected.

Other methods as described herein may be similarly modified for analysis of the protein product of expression rather than the gene transcript and related nucleic acid molecules.

Thus a further aspect of the invention provides a method of preparing a test gene transcript pattern comprising at least the steps of:

5

25

- a) releasing target polypeptides from a sample of said test organism;
- b) contacting said target polypeptides with one or more binding partners, wherein each binding partner is specific to a marker polypeptide (or a fragment thereof) encoded by the gene to which an oligonucleotide of Table 1 (or derived from a sequence described in Table 1)
- binds, to allow binding of said binding partners to said target polypeptides, wherein said marker polypeptides are specific for said disease or condition thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and
- c) assessing the target polypeptide binding to said binding partners to produce a characteristic pattern reflecting the level of gene expression of genes which express said marker polypeptides, in said test sample.

A yet further aspect of the invention provides a method of diagnosing or identifying or monitoring a disease or condition or stage thereof in an organism comprising the steps of:

- a) releasing target polypeptides from a sample of said organism;
- b) contacting said target polypeptides with one or more binding partners, wherein each binding partner is specific to a marker polypeptide (or a fragment thereof) encoded by the gene to which an oligonucleotide of Table 1 (or derived from a sequence described in Table 1)
- binds, to allow binding of said binding partners to said target polypeptides, wherein said marker polypeptides are specific for said disease or condition thereof in an

- 36 -

organism and sample thereof corresponding to the organism and sample thereof under investigation; and

5

10

15

20

25

30

35

- c) assessing the target polypeptide binding to said binding partners to produce a characteristic pattern reflecting the level of gene expression of genes which express said marker polypeptides in said sample; and
- d) comparing said pattern to a standard diagnostic pattern prepared as described hereinbefore using a sample from an organism corresponding to the organism and sample under investigation to determine the degree of correlation indicative of the presence of said disease or condition or a stage thereof in the organism under investigation.

The methods of generating standard and test patterns and diagnostic techniques rely on the use of informative oligonucleotide probes to generate the gene expression data. In some cases it will be necessary to select these informative probes for a particular method, e.g. to diagnose a particular disease, from a selection of available probes, e.g. the probes described hereinbefore (the Table 1 oligonucleotides, the Table 1 derived oligonucleotides, their complementary sequences and functionally equivalent oligonucleotides). The following methodology describes a convenient method for identifying such informative probes, or more particularly how to select a suitable sub-set of probes from the probes described herein.

Probes for the analysis of a particular disease or condition or stage thereof, may be identified in a number of ways known in the prior art, including by differential expression or by library subtraction (see for example W098/49342). As described hereinafter, in view of the high information content of most transcripts, as a starting point one may also simply analyse a random sub-set of mRNA or cDNA species and pick the most informative probes from that sub-set. The following method describes the use of immobilized

oligonucleotide probes (e.g. the probes of the invention) to which mRNA (or related molecules) from different samples is bound to identify which probes are the most informative to identify a particular type of sample, e.g. a disease sample.

5

10

25

30

35

The immobilized probes can be derived from various unrelated or related organisms; the only requirement is that the immobilized probes should bind specifically to their homologous counterparts in test organisms. Probes can also be derived from commercially available or public databases and immobilized on solid supports or, as mentioned above, they can be randomly picked and isolated from a cDNA library and immobilized on a solid support.

The length of the probes immobilised on the solid support should be long enough to allow for specific binding to the target sequences. The immobilised probes can be in the form of DNA, RNA or their modified products or PNAs (peptide nucleic acids). Preferably, the probes immobilised should bind specifically to their homologous counterparts representing highly and moderately expressed genes in test organisms. Conveniently the probes which are used are the probes described herein.

The gene expression pattern of cells in biological samples can be generated using prior art techniques such as microarray or macroarray as described below or using methods described herein. Several technologies have now been developed for monitoring the expression level of a large number of genes simultaneously in biological samples, such as, high-density oligoarrays (Lockhart et al., 1996, Nat. Biotech., 14, p1675-1680), cDNA microarrays (Schena et al., 1995, Science, 270, p467-470) and cDNA macroarrays (Maier E et al., 1994, Nucl. Acids Res., 22, p3423-3424; Bernard et al., 1996, Nucl. Acids Res., 24, p1435-1442).

In high-density oligoarrays and cDNA microarrays,

- 38 -

hundreds and thousands of probe oligonucleotides or cDNAs, are spotted onto glass slides or nylon membranes, or synthesized on biochips. The mRNA isolated from the test and reference samples are labelled by reverse transcription with a red or green fluorescent dye, mixed, and hybridised to the microarray. After washing, the bound fluorescent dyes are detected by a laser, producing two images, one for each dye. The resulting ratio of the red and green spots on the two images provides the information about the changes in expression levels of genes in the test and reference samples. Alternatively, single channel or multiple channel microarray studies can also be performed.

5

10

15

20

25

30

35

In cDNA macroarray, different cDNAs are spotted on a solid support such as nylon membranes in excess in relation to the amount of test mRNA that can hybridise to each spot. mRNA isolated from test samples is radiolabelled by reverse transcription and hybridised to the immobilised probe cDNA. After washing, the signals associated with labels hybridising specifically to immobilised probe cDNA are detected and quantified. data obtained in macroarray contains information about the relative levels of transcripts present in the test samples. Whilst macroarrays are only suitable to monitor the expression of a limited number of genes, microarrays can be used to monitor the expression of several thousand genes simultaneously and is, therefore, a preferred choice for large-scale gene expression studies.

A macroarray technique for generating the gene expression data set has been used to illustrate the probe identification method described herein. For this purpose, mRNA is isolated from samples of interest and used to prepare labelled target molecules, e.g. mRNA or cDNA as described above. The labelled target molecules are then hybridised to probes immobilised on the solid support. Various solid supports can be used for the

- 39 -

purpose, as described previously. Following hybridization, unbound target molecules are removed and signals from target molecules hybridizing to immobilised probes quantified. If radio labelling is performed, PhosphoImager can be used to generate an image file that can be used to generate a raw data set. Depending on the nature of label chosen for labelling the target molecules, other instruments can also be used, for example, when fluorescence is used for labelling, a FluoroImager can be used to generate an image file from the hybridised target molecules.

5

10

15

20

25

30

The raw data corresponding to mean intensity, median intensity, or volume of the signals in each spot can be acquired from the image file using commercially available software for image analysis. However, the acquired data needs to be corrected for background signals and normalized prior to analysis, since, several factors can affect the quality and quantity of the hybridising signals. For example, variations in the quality and quantity of mRNA isolated from sample to sample, subtle variations in the efficiency of labelling target molecules during each reaction, and variations in the amount of unspecific binding between different macroarrays can all contribute to noise in the acquired data set that must be corrected for prior to analysis.

Background correction can be performed in several ways. The lowest pixel intensity within a spot can be used for background subtraction or the mean or median of the line of pixels around the spots' outline can be used for the purpose. One can also define an area representing the background intensity based on the signals generated from negative controls and use the average intensity of this area for background subtraction.

The background corrected data can then be transformed for stabilizing the variance in the data structure and normalized for the differences in probe

5

10

15

20

25

30

35

- 40 -

intensity. Several transformation techniques have been described in the literature and a brief overview can be found in Cui, Kerr and Churchill http://www.jax.org/research/churchill/research/ expression/Cui-Transform.pdf). Normalization can be performed by dividing the intensity of each spot with the collective intensity, average intensity or median intensity of all the spots in a macroarray or a group of spots in a macroarray in order to obtain the relative intensity of signals hybridising to immobilised probes Several methods have been described in a macroarray. for normalizing gene expression data (Richmond and Somerville, 2000, Current Opin. Plant Biol., 3, p108-116; Finkelstein et al., 2001, In "Methods of Microarray Data Analysis. Papers from CAMDA, Eds. Lin & Johnsom, Kluwer Academic, p57-68; Yang et al., 2001, In "Optical Technologies and Informatics", Eds. Bittner, Chen, Dorsel & Dougherty, Proceedings of SPIE, 4266, p141-152; Dudoit et al, 2000, J. Am. Stat. Ass., 97, p77-87; Alter et al 2000, supra; Newton et al., 2001, J. Comp. Biol.,

et al 2000, supra; Newton et al., 2001, J. Comp. Biol., 8, p37-52). Generally, a scaling factor or function is first calculated to correct the intensity effect and then used for normalising the intensities. The use of external controls has also been suggested for improved normalization.

One other major challenge encountered in large-scale gene expression analysis is that of standardization of data collected from experiments performed at different times. We have observed that gene expression data for samples acquired in the same experiment can be efficiently compared following background correction and normalization. However, the data from samples acquired in experiments performed at different times requires further standardization prior to analysis. This is because subtle differences in experimental parameters between different experiments, for example, differences in the quality and quantity of

- 41 -

mRNA extracted at different times, differences in time used for target molecule labelling, hybridization time or exposure time, can affect the measured values. factors such as the nature of the sequence of transcripts under investigation (their GC content) and their amount in relation to the each other determines how they are affected by subtle variations in the experimental processes. They determine, for example, how efficiently first strand cDNAs, corresponding to a particular transcript, are transcribed and labelled during first strand synthesis, or how efficiently the corresponding labelled target molecules bind to their complementary sequences during hybridization. Batch to batch difference in the printing process is also a major factor for variation in the generated expression data.

5

10

15

20

25

30

35

Failure to properly address and rectify for these influences leads to situations where the differences between the experimental series may overshadow the main information of interest contained in the gene expression data set, i.e. the differences within the combined data from the different experimental series. Figure 1 provides one such example showing a classification based on Principal Component Analysis (PCA) of combined data from two experimental series where the main goal is to distinguish between Alzheimer/non-Alzheimer patients.

PCA (also known as singular value decomposition) is a technique for studying interdependencies and underlying relationships of a set of variables. The data are modelled in terms of a few significant factors or principal components (PC's), plus residuals. The PC's contain the main phenomena and define the systematic variability present in the data, while the residuals represent the variability interpreted as noise. Details on PCA can be found in Jollife (1986, Principal Component Analysis, Springer-Verlag, NY), and Jackson (1991, A User's Guide to Principal Components, Wiley, NY). The results of Figure 1 show that two

5

10

15

20

25

clusters are formed representing the data from two experimental series rather than the Alzheimer/non-Alzheimer differentiation. There were eight samples in common between the two series of experiments, which ideally should have fallen on top of, or in near proximity to, each other if appropriately standardized.

We have now found that gene expression data between different experiments can be efficiently standardized by including a subset of samples from one experimental series in the next experimental series and using a direct standardization method (DS), originally described by Wang and Kowalski (Anal. Chem., 1991, 63, p2750 and J. Chemometrics, 1991, 5, p129-145). Although the method of DS is well known in the field of analytical chemistry, it remains undescribed and unused in the field of gene expression data analysis.

In DS, the secondary data representing for example experimental series 2 (secondary measurements,  $R_2$ ) are corrected to match the data measured on the primary measurements representing data from series 1 ( $R_1$ ), while the calibration model remains unchanged. In DS, response matrices for both experimental series are related to each other by a transformation matrix F, i.e.

 $R_1 = R_2 F \tag{1}$ 

Where F is a square matrix dimensioned gene by gene. From (1), the transformation matrix is calculated as:

30

35

 $F = R_2^+ R_1$  (2)

The transformation matrix F in equation (2) is calculated using a relatively small subset of samples which are measured on both the master primary and the secondary series of data.

Finally, the response of the unknown sample measured on the secondary series  $r_{2,un}^T$ , is standardized

- 43 -

to the response vector  $\hat{\vec{r}}_{1,un}^{\text{T}}$  expected from the primary series

 $\hat{r}^{T}_{1,un} = rT_{21,un}\hat{F}$  (3)

5

10

15

20

25

30

35

From the preceding equation it can be seen that the column i of the transformation matrix contains the multiplication factors for a set of genes measured in the secondary series to obtain the intensity at spot i of the corrected series.

The number of samples that are repeated in the experimental series,  $R_1$  and  $R_2$ , should be equal to their ranks, which in this case is equal to the number of principal components retained for explaining the variation in the  $R_1$  and  $R_2$ . For example, if three principal components are retained for explaining the variation in the data set, a minimum of three samples should be repeated between  $R_1$  and  $R_2$ . The samples that should be repeated between different series should ideally be those that exhibit high leverages in the gene expression pattern. At times, two samples may suffice, while at other times, more than two samples should be ideally be included for good representativity. cases, the samples selected can be the same in all the experimental series to be compared (reference samples), while in other cases, representative samples can be selected sequentially by analyzing the expression pattern after each experiment. The selected samples with high leverages are then included in the next experimental series. The results of using Direct Standardization are shown in Figure 1.

Another approach for normalizing and standardizing the gene expression data set is to hybridize each DNA array with target molecules prepared from a test sample and an equal amount of labelled target molecules prepared from representative reference samples. In order to measure the intensity of labelled target

5

10

15

20

25

30

- 44 -

molecules hybridizing to the immobilized probes it is necessary that the labelled molecules are prepared from test and reference samples using different labels, for example, different fluorescent dyes can be used for preparing the labelled material. The labelled molecules prepared from reference samples can be added to the hybridization solution together with the labelled material prepared from test samples. A data file from each array representing the expression pattern of different genes in the test sample and reference samples can then be obtained, normalized and standardized by the direct standardization method as described above. instant advantage of including the differentially labelled target molecules from reference samples during hybridization is that it enables an efficient comparison of new test samples to the data sets already stored in a database.

Monitoring the expression of a large number of genes in several samples leads to the generation of a large amount of data that is too complex to be easily interpreted. Several unsupervised and supervised multivariate data analysis techniques have already been shown to be useful in extracting meaningful biological information from these large data sets. Cluster analysis is by far the most commonly used technique for gene expression analysis, and has been performed to identify genes that are regulated in a similar manner, and or identifying new/unknown tumour classes using gene expression profiles (Eisen et al., 1998, PNAS, 95, p14863-14868, Alizadeh et al. 2000, supra, Perou et al. 2000, Nature, 406, p747-752; Ross et al, 2000, Nature Genetics, 24(3), p227-235; Herwig et al., 1999, Genome Res., 9, p1093-1105; Tamayo et al, 1999, Science, PNAS, 96, p2907-2912).

In the clustering method, genes are grouped into functional categories (clusters) based on their expression profile, satisfying two criteria: homogeneity

- 45 -

- the genes in the same cluster are highly similar in expression to each other; and *separation* - genes in different clusters have low similarity in expression to each other.

Examples of various clustering techniques that have 5 been used for gene expression analysis include hierarchical clustering (Eisen et al., 1998, supra; Alizadeh et al. 2000, supra; Perou et al. 2000, supra; Ross et al, 2000, supra), K-means clustering (Herwig et al., 1999, supra; Tavazoie et al, 1999, Nature Genetics, 10 22(3), p. 281-285), gene shaving (Hastie et al., 2000, Genome Biology, 1(2), research 0003.1-0003.21), block clustering (Tibshirani et al., 1999, Tech repot Univ Stanford.) Plaid model (Lazzeroni, 2002, Stat. Sinica, 12, p61-86), and self-organizing maps (Tamayo et al. 15 1999, supra). Also, related methods of multivariate statistical analysis, such as those using the singular value decomposition (Alter et al., 2000, PNAS, 97(18), p10101-10106; Ross et al. 2000, supra) or multidimensional scaling can be effective at reducing 20

the dimensions of the objects under study.

25

30

35

However, methods such as cluster analysis and singular value decomposition are purely exploratory and only provide a broad overview of the internal structure present in the data. They are unsupervised approaches in which the available information concerning the nature of the class under investigation is not used in the analysis. Often, the nature of the biological perturbation to which a particular sample has been subjected is known. For example, it is sometimes known whether the sample whose gene expression pattern is being analysed derives from a diseased or healthy individual. In such instances, discriminant analysis can be used for classifying samples into various groups based on their gene expression data.

In such an analysis one builds the classifier by training the data that is capable of discriminating

- 46 **-**

between member and non-members of a given class. trained classifier can then be used to predict the class of unknown samples. Examples of discrimination methods that have been described in the literature include Support Vector Machines (Brown et al, 2000, PNAS, 97, p262-267), Nearest Neighbour (Dudoit et al., 2000, supra), Classification trees (Dudoit et al., 2000, supra), Voted classification (Dudoit et al., 2000, supra), Weighted Gene voting (Golub et al. 1999, supra), and Bayesian classification (Keller et al. 2000, Tec report Univ of Washington). Also a technique in which PLS (Partial Least Square) regression analysis is first used to reduce the dimensions in the gene expression data set followed by classification using logistic discriminant analysis and quadratic discriminant analysis (LD and QDA) has recently been described (Nguyen & Rocke, 2002, Bioinformatics, 18, p39-50 and 1216-1226).

5

10

15

A challenge that gene expression data poses to 20 classical discriminatory methods is that the number of genes whose expression are being analysed is very large compared to the number of samples being analysed. However in most cases only a small fraction of these genes are informative in discriminant analysis problems. 25 Moreover, there is a danger that the noise from irrelevant genes can mask or distort the information from the informative genes. Several methods have been suggested in literature to identify and select genes that are informative in microarray studies, for example, 30 t-statistics (Dudoit et al, 2002, J. Am. Stat. Ass., 97, p77-87), analysis of variance (Kerr et al., 2000, PNAS, 98, p8961-8965), Neighbourhood analysis (Golub et al, 1999, supra), Ratio of between groups to within groups sum of squares (Dudoit et al., 2002, supra), Non parametric scoring (Park et al., 2002, Pacific Symposium 35 on Biocomputing, p52-63) and Likelihood selection (Keller et al., 2000, supra).

- 47 -

In the methods described herein the gene expression data that has been normalized and standardized is analysed by using Partial Least Squares Regression (PLSR). Although PLSR is primarily a method used for regression analysis of continuous data (see Appendix A), 5 it can also be utilized as a method for model building and discriminant analysis using a dummy response matrix based on a binary coding. The class assignment is based on a simple dichotomous distinction such as breast cancer (class 1) / healthy (class 2), or a multiple 10 distinction based on multiple disease diagnosis such as breast cancer (class 1) / Alzheimer (class 2) / healthy (class 3). The list of diseases for classification can be increased depending upon the samples available 15 corresponding to other diseases or conditions or stages thereof.

PLSR applied as a classification method is referred to as PLS-DA (DA standing for Discriminant analysis). PLS-DA is an extension of the PLSR algorithm in which the Y-matrix is a dummy matrix containing n rows 20 (corresponding to the number of samples) and K columns (corresponding to the number of classes). The Y-matrix is constructed by inserting 1 in the kth column and -1 in all the other columns if the corresponding ith object 25 of X belongs to class k. By regressing Y onto X, classification of a new sample is achieved by selecting the group corresponding to the largest component of the fitted,  $\hat{y}(x) = (\hat{y}_1(x), \hat{y}_2(x), \dots, \hat{y}_k(x))$ . Thus, in a -1/1 response matrix, a prediction value below 0 means that the sample belongs to the class designated as -1, 30 while a prediction value above 0 implies that the sample belongs to the class designated as 1.

An advantage of PLSR-DA is that the results obtained can be easily represented in the form of two different plots, the score and loading plots. Score plots represent a projection of the samples onto the principal components and shows the distribution of the

35

- 48 -

samples in the classification model and their relationship to one another. Loading plots display correlations between the variables present in the data set.

5

10

15

It is usually recommended to use PLS-DA as a starting point for the classification problem due to its ability to handle collinear data, and the property of PLSR as a dimension reduction technique. Once this purpose has been satisfied, it is possible to use other methods such as Linear discriminant analysis, LDA, that has been shown to be effective in extracting further information, Indahl et al. (1999, Chem. and Intell. Lab. Syst., 49, p19-31). This approach is based on first decomposing the data using PLS-DA, and then using the scores vectors (instead of the original variables) as input to LDA. Further details on LDA can be found in Duda and Hart (Classification and Scene Analysis, 1973, Wiley, USA).

The next step following model building is of model 20 validation. This step is considered to be amongst the most important aspects of multivariate analysis, and tests the "goodness" of the calibration model which has In this work, a cross validation approach been built. has been used for validation. In this approach, one or 25 a few samples are kept out in each segment while the model is built using a full cross-validation on the basis of the remaining data. The samples left out are then used for prediction/classification. Repeating the simple cross-validation process several times holding 30 different samples out for each cross-validation leads to a so-called double cross-validation procedure. approach has been shown to work well with a limited amount of data, as is the case in some of the Examples described here. Also, since the cross validation step 35 is repeated several times the dangers of model bias and overfitting are reduced.

Once a calibration model has been built and

validated, genes exhibiting an expression pattern that is most relevant for describing the desired information in the model can be selected by techniques described in the prior art for variable selection, as mentioned elsewhere. Variable selection will help in reducing the final model complexity, provide a parsimonious model, and thus lead to a reliable model that can be used for prediction. Moreover, use of fewer genes for the purpose of providing diagnosis will reduce the cost of the diagnostic product. In this way informative probes which would bind to the genes of relevance may be identified.

We have found that after a calibration model has been built, statistical techniques like Jackknife (Effron, 1982, The Jackknife, the Bootstrap and other resampling plans. Society for Industrial and Applied mathematics, Philadelphia, USA), based on resampling methodology, can be efficiently used to select or confirm significant variables (informative probes).

The approximate uncertainty variance of the PLS regression coefficients B can be estimated by:

$$S^{2}B = \sum_{m=1}^{M} ((B-B_{m})g)^{2}$$

where

15

20

25

30

 $S^2B$  = estimated uncertainty variance of B;

B = the regression coefficient at the cross validated rank A using all the N objects;

 $B_m$  = the regression coefficient at the rank A using all objects except the object(s) left out in cross validation segment m; and

g = scaling coefficient (here: g=1).

In our approach, Jackknife has been implemented together with cross-validation. For each variable the difference between the B-coefficients B<sub>i</sub> in a

cross-validated sub-model and  $B_{\rm tot}$  for the total model is first calculated. The sum of the squares of the differences is then calculated in all sub-models to obtain an expression of the variance of the  $B_{\rm i}$  estimate for a variable. The significance of the estimate of  $B_{\rm i}$  is calculated using the t-test. Thus, the resulting regression coefficients can be presented with uncertainty limits that correspond to 2 Standard Deviations, and from that significant variables are detected.

5

10

15

20

25

30

35

No further details as to the implementation or use of this step are provided here since this has been implemented in commercially available software, The Unscrambler, CAMO ASA, Norway. Also, details on variable selection using Jackknife can be found in Westad & Martens (2000, J. Near Inf. Spectr., 8, pl17-124).

The following approach can be used to select informative probes from a gene expression data set:

- a) keep out one unique sample (including its repetitions if present in the data set) per cross validation segment;
- b) build a calibration model (cross validated segment) on the remaining samples using PLSR-DA;
- c) select the significant genes for the model in step b) using the Jackknife criterion;
- d) repeat the above 3 steps until all the unique samples in the data set are kept out once (as described in step a). For example, if 75 unique samples are present in the data set, 75 different calibration models are built resulting in a collection of 75 different sets of significant probes;
- e) select the most significant variables using the frequency of occurrence criterion in the generated sets of significant probes in step d). For example, a set of probes appearing in all sets (100%) are more informative than probes appearing in only 50% of the

- 51 -

generated sets in step d).

5

10

15

20

25

30

35

Once the informative probes for a disease have been selected, a final model is made and validated. most commonly used ways of validating the model are cross-validation (CV) and test set validation. cross-validation, the data is divided into k subsets. The model is then trained k times, each time leaving out one of the subsets from training, but using only the omitted subset to compute error criterion, RMSEP (Root Mean Square Error of Prediction). If k equals the sample size, this is called "leave-one-out" crossvalidation. The idea of leaving one or a few samples out per validation segment is valid only in cases where the covariance between the various experiments is zero. Thus, one sample at-a-time approach can not be justified in situations containing replicates since keeping only one of the replicates out will introduce a systematic bias in our analysis. The correct approach in this case will be to leave out all replicates of the same samples at a time since that would satisfy assumptions of zero covariance between the CV-segments.

The second approach for model validation is to use a separate test-set for validating the calibration model. This requires running a separate set of experiments to be used as a test set. This is the preferred approach given that real test data are available.

The final model is then used to identify a disease, condition or stage thereof in test samples. For this purpose, expression data of selected informative genes is generated from test samples and then the final model is used to determine whether a sample belongs to a diseased or non-diseased class or has a condition or stage thereof.

Thus viewed from a yet further aspect the present invention provides a method of identifying probes useful for diagnosing or identifying or monitoring a disease or

- 52 -

condition or stage thereof in an organism, comprising the steps of:

5

10

15

20

25

30

35

- a) immobilizing a set of oligonucleotide probes, preferably as described hereinbefore, on a solid support;
- b) isolating mRNA from a sample of a normal organism (normal sample), which may optionally be reverse transcribed to cDNA;
- c) isolating mRNA from a sample from an organism, corresponding to the sample and organism of step (b), which is known to have said disease or condition or a stage thereof (diseased sample), which may optionally be reverse transcribed to cDNA;
- d) hybridizing the mRNA or cDNA of steps (b) and(c) to said set of immobilized oligonucleotide probes of step (a); and
- e) assessing the amount of mRNA or cDNA hybridizing to each of said oligonucleotide probes to determine the level of gene expression of genes to which said oligonucleotide probes bind in said normal and diseased samples to generate a gene expression data set for each sample;
- f) normalizing and standardizing said data set of step (e);
- g) constructing a calibration model for classification, preferably using the statistical techniques Partial Least Squares Discriminant Analysis (PLS-DA) and Linear Discriminant Analysis (LDA);
- h) performing JackKnife analysis and identifying those oligonucleotide probes which are required for classification of said disease and normal samples into their respective groups.

Preferably a model for classification purposes is

- 53 -

generated by using the data relating to the probes identified according to the above described method. Preferably the sample is as described previously. Preferably the oligonucleotides which are immobilized in step (a) are randomly selected as described below or are the probes as described hereinbefore. Such oligonucleotides may be of considerable length, e.g. if using cDNA (which is encompassed within the scope of the term "oligonucleotide"). The identification of such cDNA molecules as useful probes allows the development of shorter oligonucleotides which reflect the specificity of the cDNA molecules but are easier to manufacture and manipulate.

5

10

15

20

25

30

35

The above described model may then be used to generate and analyse data of test samples and thus may be used for the diagnostic methods of the invention. In such methods the data generated from the test sample provides the gene expression data set and this is normalized and standardized as described above. This is then fitted to the calibration model described above to provide classification.

The method described herein can also be used to simultaneously select informative probes for several related and unrelated diseases or conditions. Depending upon which diseases or conditions have been included in the calibration or training set, informative probes can be selected for the said diseases or conditions. The informative probes selected for one disease or condition may or may not be similar to the informative probes selected for another disease or condition of interest. It is the pattern with which the selected genes are expressed in relation to each other during a disease, condition, or stage thereof, that determines whether or not they are informative for the disease, condition or stage thereof.

In other words, informative genes are selected based on how their expression correlates with the

- 54 -

expression of other selected informative genes under the influence of responses generated by the disease, condition or stage thereof under investigation. In examples 1 and 2 provided hereinafter, 139 informative probes were selected for breast cancer diagnosis and 182 probes were selected for Alzheimer's disease diagnosis by training the gene expression data set of genes representing 1435 or 758 randomly picked cDNA clones for breast cancer/non breast cancer samples, or Alzheimer/non-Alzheimer samples, respectively. Among the probes selected for breast cancer and Alzheimer, about 10 probes were informative both for breast cancer and Alzheimer disease diagnosis.

5

10

35

For the purpose of isolating informative probes or 15 identifying several related and unrelated diseases, conditions and stages thereof simultaneously, the gene expression data set must contain the information on how genes are expressed when the subject has a particular disease, condition or stage thereof under investigation. 20 The data set is generated from a set of healthy or diseased samples, where a particular sample may contain the information of only one disease, condition or stages thereof or may also contain information about multiple diseases, conditions or stages thereof. For example, if 25 the isolation of informative probes for Alzheimer disease, breast cancer and diabetes is sought, whole blood samples can be obtained from an Alzheimer patient who has breast cancer and diabetes. Hence, the method also teaches an efficient experimental design to reduce the number of samples required for isolating informative 30 probes by selecting samples representing more than one disease, condition or stage thereof.

As mentioned previously, in view of the high information content of most transcripts, the identification and selection of informative probes for use in diagnosing, monitoring or identifying a particular disease, condition or stage thereof may be

- 55 -

dramatically simplified. Thus the pool of genes from which a selection may be made to identify informative probes may be radically reduced.

5

10

15

20

25

30

35

Unlike, in prior art technologies where informative probes are selected from a population of thousands of genes that are being expressed in a cell, like in microarray, in the method described herein, the informative probes are selected from a limited number of randomly obtained genes. For example, from a population of 1435 cDNA clones, randomly picked from a human whole blood cDNA library, we were able to select 139 informative probes for breast cancer diagnosis (see Example 1 and Table 2).

Thus in a preferred aspect of the above mentioned method of identifying probes useful for diagnosing or identifying or monitoring a disease or condition or stage thereof in an organism, said set of oligonucleotides which are immobilized in step (a) are randomly selected from a larger set of oligonucleotides, e.g. from a cDNA library or other oligonucleotide pool, which may be, but is preferably not selected from the set provided herein. Preferably said larger set comprises oligonucleotides which correspond to moderately or highly expressed genes. Thus preferably in methods of the invention, the set of oligonucleotides according to the invention are replaced with a set of oligonucleotides which are randomly selected, e.g. from commercially available oligonucleotide or cDNA libraries.

As referred to herein "random" refers to selection which is not biased based on the extent of information carried by the transcripts in relation to the disease, condition or organism under study, ie. without bias towards their likely utility as informative probes.

Whilst a random selection may be made from a pool of transcripts (or related products) which have been biased, e.g. to highly or moderately expressed

5

10

15

20

transcripts, preferably random selection is made from a pool of transcripts not biased or selected by a sequence-based criterion. The larger set may therefore contain oligonucleotides corresponding to highly and moderately expressed genes, or alternatively, may be enriched for those corresponding to the highly and moderately expressed genes.

Random selection from highly and moderately expressed genes can be achieved in a wide variety of A strategy used in this work, but not limiting in itself involves randomly picking a significant number of cDNA clones from a cDNA library constructed from a biological specimen under investigation. Since, in a cDNA library, the cDNA clones corresponding to transcripts present in high or moderate amount are more frequently present than transcripts corresponding to cDNA present in low amount, the former will tend to be picked up more frequently than the latter. A pool of cDNA enriched for those corresponding to highly and moderately expressed genes can be isolated by this approach.

To identify genes that are expressed in high or moderate amount among the isolated population for use in methods of the invention, the information about the 25 relative level of their transcripts in samples of interest can be generated using several prior art Both non-sequence based methods, such as differential display or RNA fingerprinting, and sequence-based methods such as microarrays or 30 macroarrays can be used for the purpose. Alternatively, specific primer sequences for highly and moderately expressed genes can be designed and methods such as quantitative RT-PCR can be used to determine the levels of highly and moderately expressed genes. Hence, a 35 skilled practitioner may use a variety of techniques which are known in the art for determining the relative level of mRNA in a biological sample.

- 57 -

Especially preferably the sample for the isolation of mRNA in the above described method is as described previously and is preferably not from the site of disease and the cells in said sample are not disease cells and have not contacted disease cells.

The following examples are given by way of illustration only in which the Figures referred to are as follows:

5

35

Figure 1 shows the effect of Direct Standardization (DS) on the Alzheimer data measured in two different 10 series of experiments in which AD denotes Alzheimer's samples and A,B are non-Alzheimer's samples. samples in both series have been labelled systematically as (xx 7/xx 8), whereas the corrected samples from 15 series 8 (in b,c,d) have been labelled as (xx c), thus, for example, AD2-7 denotes Alzheimer disease sample number 2 in experiment series 7. The circled spots represent the samples chosen as the transfer samples. The connecting lines in figures b,c,d show the proximity of the replicated samples after applying DS. 20 lines in figures a,c,d represent the decision boundary separating the classes. These lines have not been drawn on the basis of any statistical criteria, but serve the purpose of visually separating the classes. 25 four figures show scores plot (PC1-PC2) from PCA analysis based on (a) non-standardized data, (b) scores plot after direct standardization using 3 transfer samples, (c) scores plot after direct standardization using 4 transfer sample, (d) scores plot after direct 30 standardization using 8 transfer samples;

Figure 2 shows the projection of normal (including benign) and breast cancer samples onto a classification model generated by PLSR-DA using the data of 44 informative genes, in which PC is the principal components and N and C are normal and breast cancer samples, respectively;

Figure 3 shows the projection of individuals with

- 58 -

and without Alzheimer's disease onto a classification model generated by PLSR-DA using 182 informative genes;

Figures 4, 6 and 8 show projection plots as Figure 2 in which the classification model is generated using 719, 111 and 345 cDNAs, respectively, wherein PC is the principal components, N denotes normal and B denotes breast cancer samples;

Figures 5, 7 and 9 show prediction plots based on 3 principal components using the data of 719, 111 and 345 cDNAs, respectively;

Figure 10 shows a projection plot as Figure 3 in which the classification model is generated using 520 cDNAs; and

Figure 11 is the prediction plot corresponding to Figure 10.

## Example 1: Diagnosis of Breast Cancer

### Methods

20

25

30

35

5

10

Whole blood was obtained from the arms of breast cancer patients and patients with benign tumours (Ullevål and Haukland hospitals in Norway). All of the patients with breast cancer had a malignant tumour of the breast (disease samples). Healthy blood was collected from the above two hospitals, or collected at a Health station at Ås, Norway or at DiaGenic AS, Norway, from the arms of female donors with no reported signs of breast cancer. The blood from healthy individuals or with benign tumours comprise the normal samples. The blood was either collected in tubes containing EDTA and stored immediately at -80°C or was collected in PAXgene tubes and stored for 12-24 hours at room temperature before finally storing them at -80°C before use. Further details of the breast cancer and benign tumour patients from which blood was taken is provided in Table 5.

- 59 -

mRNA was isolated from the blood of the 29 breast cancer patients and 46 normal donors and used to prepare labelled probes by reverse transcribing in the presence of  $\alpha^{33}P$ -dATP. The first strand cDNA of the normal and diseased samples was bound, separately to 1435 cDNA clones immobilized on a solid support (nylon membrane). These cDNA clones were randomly picked, without any prior knowledge of their gene sequences, from a cDNA library constructed using whole blood of 550 healthy individuals (Clontech, Palo Alto, USA). These methods were conducted as follows.

5

10

For amplification of inserts, bacterial clones were grown in microtiter plates containing 150  $\mu$ l LB with 50 15  $\mu$ g/ml carbenicillin, and incubated overnight with agitation at 37°C. To lyse the cells, 5  $\mu$ l of each culture were diluted with 50  $\mu$ l H2O and incubated for 12 min. at 95°C. Of this mixture, 2  $\mu$ l were subjected to a PCR reaction using 20 pmoles of M13 forward and reverse 20 primer in presence of 1.5 mM MqCl<sub>2</sub>. PCR reactions were performed with the following cycling protocol: 4 min. at 95°C, followed by 25 cycles of 1 min. at 94°C, 1 min. at 60°C and 3 min. at 72°C either in a RoboCycler® Temperature Cycler (Stratagene, La Jolla, USA) or DNA 25 Engine Dyad Peltier Thermal Cycler (MJ Research Inc., Waltham, USA). The amplified products were denatured by incubating with NaOH (0.2 M, final concentration) for 30 min. and spotted onto Hybond-N+ membranes (Amersham Pharmacia Biotech, Little Chalfont, UK), using MicroGrid 30 II workstation according to the manufacturer's instructions (BioRobotics Ltd, Cambridge England). The immobilized cDNAs were fixed using a UV cross-linker (Hoefer Scientific Instruments, San Francisco, USA).

In addition to the 1435 cDNAs, the printed arrays also contained controls for assessing background level, consistency and sensitivity of the assay. These were

- 60 -

spotted at multiple positions and included controls such as PCR mix (without any insert); positive and negative controls of SpotReportTM 10 array validation system (Stratagene, La Jolla, USA) and cDNAs corresponding to constitutively expressed genes such as b-actin, g-actin, GAPDH, HOD and cyclophilin. Also, oligonucleotides corresponding to SIX1, b-tubulin, TRP-2, MDM2, Myosin Light C, CD44, Maspin, Laminin, and SRP 19 were included to detect disseminated cancer cells.

10

15

20

25

30

35

5

The total RNA from blood collected in EDTA tubes was purified using Trizol LS Reagent protocol (Invitrogen/Life Technologies). From blood contained in PAXgene tubes, the total RNA was purified according to the supplier's instructions (PreAnalytiX, Hombrechtikon, Switzerland). Contaminating DNA was removed from the isolated RNA by DNAase I treatment using DNA-free kit (Ambion, Inc. Austin, USA). RNA quality was determined visually by inspecting the integrity of 28S and 18S ribosomal bands following agarose gel electrophoresis. The concentration and purity of extracted RNA was determined by measuring the absorbance at 260 nm and 280 nm. mRNA was isolated from the total RNA using Dynabeads as per the supplier's instructions (Dynal AS, Oslo, Norway).

Labelling and hybridization experiments were performed in batches. The number of samples assayed in each batch varied from six to nine. In the case of samples that were assayed more than once (replicates), aliquots derived from the same mRNA pool were used for probe synthesis. For probe synthesis, aliquots of mRNA corresponding to 4-5  $\mu$ g of total RNA were mixed together with oligodT<sub>25NV</sub> (0.5  $\mu$ g/ml) and mRNA spikes of SpotReport<sup>TM</sup> 10 array validation system (10 pg; Spike 2, 1 pg), heated to 70°C to remove secondary structures, and then chilled on ice. Probes were prepared in 35 $\mu$ 1

- 61 -

reaction mixes by reverse transcription in the presence of  $50\mu\text{Ci}$  [ $\alpha^{33}\text{P}$ ] dATP, 3.5  $\mu\text{M}$  dATP, 0.6 mM each of dCTP, dTTP, dGTP, 200 units of SuperScript reverse transcriptase (Invitrogen, LifeTechnologies) and 0.1 M DTT, labelling for 1.5 hr at 42°C. Following synthesis, the enzyme was deactivated for 10 min. at 70°C and mRNA removed by incubating the reaction mix for 20 min. at 37°C in 4 units of Ribo H (Promega, Madison USA). Unincorporated nucleotides were removed using ProbeQuant G 50 Columns (Amersham Biosciences, Piscataway, USA).

5

10

25

30

Prior to hybridization, the membranes were equilibrated in 4 x SSC for 2 hr at room temperature and prehybridized overnight at 65°C in 10 ml

15 prehybridisation solution (4 x SSC, 0.1 M NaH<sub>2</sub>PO<sub>4</sub>, 1 mM EDTA, 8% dextran sulphate, 10 x denhardt's solution, 1% SDS). Freshly prepared probes were added to 5 ml of the same prehybridisation solution, and hybridization continued overnight at 65°C. The membranes were washed at 65°C at increasing stringency (2 x 30 min. each in 2 x SSC, 0.1% SDS; 1 x SSC, 0.1% SDS; 0.1 x SSC, 0.1% SDS) to remove unspecific signals.

The amount of labelled first strand cDNA binding to each spot was assessed and quantified using a Phospholmager to generate a gene expression data set. The data was generated using Phoretix software version 3 (Non Linear Dynamics, England). Background subtraction was performed on the generated data by subtracting the median of the line of pixels around each spot outline from the total intensity obtained from the respective spots.

The background-subtracted data was then normalized and transformed by selecting out 50 lowest and 50 maximum signals from each membrane. This step was to exclude genes that were expressed with a high degree of

- 62 -

variance. Since the genes varied from membrane to membrane, the expression data from 497 genes were removed from the data set. The values for the remaining 938 genes were then normalised by using different approaches such as external controls, dividing each spot by the median intensity of the observed signal in the respective membrane, range normalizing the data from each membrane, and then log transforming the data obtained.

10

15

20

25

30

35

5

The processed data obtained above was then used to isolate the informative probes by:

- a) keeping one unique sample (including all repetitions of the selected sample) out per cross validation segment;
- b) building a calibration model (cross validated)on the remaining samples using PLSR-DA;
- c) selecting the set of significant genes for the model in step b using the Jackknife criterion;
- d) repeating steps a), b) and c) until all the unique samples were kept out once (hence, in all 75 different calibration models were built (after repeating step b) 75 times), resulting in 75 different sets of significant probes (after repeating step c) 75 times));
- e) selecting significant variables using the frequency of occurrence criterion amongst the 75 different sets of significant probes.

The selected informative probes based on occurrence criterion were used to construct a classification model. The result of the classification model based on probes appearing in at least 90% of the generated sets after the step of isolating informative probes as described above is shown in Figure 2 in which it is seen that the expression pattern of these genes was able to classify most women with breast cancer and women with no breast cancer into distinct groups. In this figure PC1 and PC2

- 63 -

indicate the two principal components statistically derived from the data which best define the systemic variability present in the data. This allows each sample, and the data from each of the informative probes to which the sample's labelled first strand cDNA was bound, to be represented on the classification model as a single point which is a projection of the sample onto the principal components - the score plot.

5

20

25

30

35

The ability of the generated model, based on isolated informative probes, to predict future samples was determined by the double cross-validation approach. The performance of the diagnostic test for breast cancer based on the occurrence criterion is presented in Table 6.

Correct prediction of most breast cancer cells was achieved. These included all three samples obtained from women with ductal carcinoma in situ (DCIS), 11/15 samples obtained from women with stage I breast cancer, all five samples obtained from women with stage II breast cancer, and one of two samples obtained from women with stage III breast cancer. Interestingly, two correctly predicted stage I samples were obtained from women having a tumour size of <5 mm in diameter.

The model also correctly predicted the class of most non-cancer samples (41/46), including those that were obtained from women with non-cancerous breast abnormalities.

Confirmation that the gene transcripts are not from cells which are disseminated disease cells has been confirmed by several lines of evidences. Firstly, the informative genes were expressed constitutively at high or moderate levels in blood cells of women irrespective of whether they had cancer or not. Secondly, in the

- 64 -

assay described in this Example, in order to identify transcripts, at least 720 disseminated cells in blood samples would be required. Since, the average number of disseminated cells present in blood during different stages of breast cancer is much lower (organ confined breast cancer, 0.8 cells per ml; invasive breast cancer spread to lymph nodes only, 2.4 cells per ml; and metastatic breast cancer, 6 cells per ml; SD>100%) (29), we believe that the signals being detected originated from peripheral blood cells and could not have originated from disseminated cells. Thirdly, we were not able to detect any signal from the eight cancer markers known to have elevated expression in malignant cancer cells, including cancer cells that are disseminated in the blood.

## Example 2: Diagnosis of Alzheimer's disease

5

10

15

30

35

Similar experiments were conducted with samples from
Alzheimer's patients. In this method 7 patients
diagnosed with Alzheimer's Disease at the Memory Clinic
at Ullevål University Hospital were used in the trial.
The patients were confirmed as having Alzheimer's
disease based on the following criteria:

- 25 \* A standardized interview with a care-giver using IQCODE, an ADL scale and a scale measuring behaviour of the patient (Green scale).
  - \* Neuropsychological evaluation using MMSE, Clock drawing test, Trailmaking test A and B (TMT A and B), Kendrick object learning test (visual memory test), part of the Wechsler battery and Benton test.
  - \* A psychiatric evaluation using scales for detection of depression, MADRS for interviewing the patient and Cornell scale for interviewing the care-giver.
  - \* A physical examination.
  - \* Laboratory tests of blood samples to rule out other

- 65 -

diseases.

20

25

30

35

- \* CT scan of the brain.
- \* SPECT of the brain.

The mean age of the patients was 72.3 with an age range of 69-76. The mean MMSE score was 22.0 (the maximum score attainable being 30).

Six age-matched individuals without diagnosed

Alzheimer's disease were used as a control. All had been tested with MMSE and had a minimum score of 28 (mean: 28.4). The mean age of the normal control group was 73.0 and the age range 66-81. A sample from a 16-year old individual, with a consequent minimal chance of having Alzheimer's disease, was also included as an additional control.

Using the methods described above (except that hybridization to 758 rather than 1435 cDNA clones was performed), informative probes were selected based on occurrence criterion and used to construct a The results of the classification classification model. model based on probes appearing at least once in the generated sets after the method to isolate informative probes as described above is shown in Figure 3 in which it will be seen that the expression pattern of these genes was able to classify individuals with or without Alzheimer's disease into distinct groups. Figure PC1 and PC2 indicate the 2 principal components statistically derived from the data which define the systematic variability present in the data. each sample, and the data from each of the informative probes to which the samples' cDNA was bound, to be represented on the classification model as a single point which is a projection of the sample onto the principal components - the score plot.

5

The ability of the generated model, based on isolated informative probes, to predict future samples was determined by the double cross-validation. The performance of the diagnostic test for Alzheimer's disease is presented in Table 7.

## Appendix A

Partial Least Squares regression (PLSR)

5 Let a multivariate regression model be defined as:

Y = XB + F

where

X a NxP matrix with N predictor variables (genes);
Y (NxJ) being the J predicted variables. In our case Y represents a matrix containing dummy variables;
B is a matrix of regression coefficients; and
F is a NxJ matrix of residuals.

15

The structure of the PLSR model can be written as:

 $X = TP^{T} + E_{A}$ , and  $Y = TQ^{T} + F_{A}$ , where

20

where

T (NxA) is a matrix of score vectors which are linear combinations of the x-variables;

P (PxA) is a matrix with the x-loading vectors  $p_a$  as columns;

Q (JxA) is a matrix with the y-loading vectors  $q_a$  as columns;

 $E_a$  (NxP) is the matrix for X after A factors; and  $F_a$  (NxJ) is the matrix for Y after A factors.

30

35

25

The criterion in PLSR is to maximize the explained covariance of [X,Y]. This is achieved by the loading weights vector  $w_{a+1}$ , which is the first eigenvector of  $E_a{}^TF_aF_a{}^TE_a$  ( $E_a$  and  $F_a$  are the deflated X and Y after a factors or PLS components).

The regression coefficients are given by:

5

$$B = W(P^{T}W)^{-1}Q^{T}$$

A PLSR model with full rank, i.e. maximum number of components, is equivalent to the MLR solutions. Further details on PLSR can be found in Marteus & Naes, 1989, Multivariate Calibration, John Wiley & Sons, Inc., USA and Kowalski & Seasholtz, 1991, supra.

- 69 -

## Example 3: Validation of Example 1, diagnosis of breast cancer

The results in Example 1 were validated by using the informative probes identified in Example 1 on new beast cancer and control samples.

#### <u>Methods</u>

5

The methods, essentially as described in Example 1, were used. Blood was taken from patients as described in Table 8. However, blood was collected in PAXgene tubes and the first strand labelled cDNAs were hybridized to 719 cDNAs spotted on nylon membranes along with other controls as described in Example 1. After background subtraction using control spots, the data of each membrane was normalized using the inter quantile range. The data was analysed as described in Example 1 and the model validated by cross validation.

The 719 cDNAs which were spotted are a subset of the cDNAs spotted in Example 1 and include 111 cDNAs described in Table 2 and which were found to be informative in Example 1.

#### 25 Results

30

35

The results are shown in Figures 4 to 9. Figures 4, 6 and 8 are projection plots similar to Figure 2 and show the projection of normal and breast cancer patients' samples onto a classification model generated using all 719 cDNA. Figure 6 is similar but uses a classification model generated with the 111 probes common to Example 1. Figure 8 uses the 345 sequences of the 719 for which sequence information is provided herein. In each case classification of normal and breast cancer groups was possible. Figures 5, 7 and 9 show prediction plots which reflect the ability of the generated models to correctly diagnose breast cancer. In the 3 prediction

plots shown, the disease samples appear on the x axis at +1 and the non-disease samples appear at -1. The y axis represents the predicted class membership. During prediction, if the prediction is correct, disease samples should fall above zero and non-disease samples should fall below zero. In each case almost all samples are correctly predicted.

# Example 4: Validation of Example 2, diagnosis of Alzheimers

The results in Example 2 were validated by using the informative probes identified in Example 2 on new Alzheimer's patient samples.

15

20

30

35

10

5

## Methods

The methods, essentially as described in Example 2, were used. Twelve female patients diagnosed with Alzheimer's disease at the Memory Clinic at Ullevål University Hospital who were confirmed as having Alzheimer's disease based on the criteria of Example 2 were used in

the trial. The mean age of the patients was 72.3 with an age range of 66-83. The mean MMSE score was 22.0 (the maximum score attainable being 30)

(the maximum score attainable being 30).

Sixteen age-matched female individuals without diagnosed Alzheimer's disease were used as the normal control group. All had been tested with MMSE and had a minimum score of 29. The mean age of the normal control group was 74.0 and the age range 66-86.

After transfer of the blood to PAXgene tubes, total mRNA was isolated from the blood of the Alzheimer's disease and from the control group donors according to the manufacturers's instructions (PreAnalytiX, Hombrechtikon, Switzerland). The isolated mRNA was labelled during reverse transcription in the presence of

 $\alpha^{33}$ P-dATP, yielding a labelled first strand cDNA. Hybridization was performed as described previously onto 730 cDNA clones picked from a cDNA library from whole blood of 550 healthy individuals without knowledge of the gene sequence of the random cDNA clones.

## Results

5

The results are shown in Figures 10 and 11. Figure 10 is a projection plot generated using 520 probes which have been sequenced. Figure 11 is a prediction plot and shows correct prediction of almost all samples.

Table 1a

## List of probes informative for disease diagnosis

		Sequence	No. of
	Clone ID	ID	nucleotides
1	1-01		Tablootiaco
2	1-02		
3	1-13		
4	1-21	-	•
5	1-24	308	373
6	1-28	310	564
7	1-30	1180	622
8	1-34	313	554
9	I-37	<b>-</b> :.	
10	1-42	-	•
11	<b>I-52</b>	-	•
12	1-54	1181	155
13	1-58	326	554
14	1-71	-	
15	1-72	-	_
16	1-86	•	
17	I-95		
18	11-03	361	622
19	11-05	363	628
20	11-06	364	528
21	11-10	368	329
22	11-24	381	534
23	11-25	382	444
24	11-26	383	566
25	II-33 II-34	390	523
26		391	566
27	11-41	397	534
28 29	11-42 11-47	398	512
30	11-57	411	505
30	II-61	415	596
32	11-69	423	387
33	11-09	424	420
34	11-75	429	535
35	11-83	- 429	333
36	11-84	438	577
37	11-87	441	
38	11-88	442	552 606
39	11-90	442	
40	11-94	448	329
41	111-02	453	. 747
42	111-05	700	
43	111-06	458	682
43	מטיווו	450	002

	T 111 66	7	~
44	111-08	460	536
45	111-10	<del> </del>	
. 46	III-13	464	615
47	111-15	<u> </u>	-
48	111-17		-
49	111-20	1183	479
50	111-23	473	694
51	111-26	476	476
52	111-35	485	551
53	111-39	487	224
54	111-40	488	349
55	111-43	490	382
· 56	111-44	491	382
57	111-53	500	390
58	111-56	503	109
59	111-57	504	374
60	111-60	-	-
61	111-60	-	
62	111-61	507	521
63	111-63	509	575
64	111-68		
65	111-74	518	502
66	111-80	523	585
67	111-82	-	-
68	JII-85	526	516
69	111-89	530	660
70	111-92		
71	111-96	-	•
72	IV-14	684	545
73	IV-15	7185	628
74	IV-23		
76	IV-26	1186	494
75	IV-26		-
77	IV-29		<u> </u>
78	IV-31	687	268
79	IV-32	688	569
80	IV-34		
B1	IV-35		
82	IV-41		
83	IV-45		•
84	IV-53	61	362
85	IV-62	-	
86	IV-69	192	286
87	IV-80	701	579
88	. IV-82	-	
89	IV-93		-
90	IX-10	736	641
91	IX-12	•	-
92	IX-38	757	583
93	· IX-39	758	424
· 94	IX-42	-	-
95	IX-4B	764 ·	626
96	IX-77	785	556
97	V-01	-	•
98	V-02		
99	V-03	706	496
			700

	1 1/2/		
100	V-04	707	397
101	V-06		<u> </u>
102	V-07	708	293
103	V-11	1188	599
104	V-12	711	498
105	V-15	-	-
106	V-17	•	
107	V-21		
108	V-25	-	•
109	V-32	-	-
110	V-35	-	-
111	V-39	-	-
112	V-42	-	-
113	V-43	-	-
114	V-47	<del>                                     </del>	
115	V-49	-	
116	V-52	<u> </u>	
117	V-54	<del> </del>	
118	V-55	77	412
		· · · · · · · · · · · · · · · · · · ·	
119	V-58		
120	V-59		
121	V-65		
122	V-68		
123	V-71		·
124	V-75		
125	V-79		
126	V-80	726	260
127	V-90		-
128	V-91	-	•
129	V-92	-	•
130	V-94	-	•
131	VI-02	-	
132	VI-04	865	122
133	VI-07	93	405
134	VI-09	-	-
135	VI-10	-	-
136	VI-12	869	667
137	VI-14	871	642
138	VI-17	-	
139	VI-20	876	115
140	VI-21	-	• •
141	VI-23	87B	634
142	VI-34		-
143	VI-41		
144	VI-42	-	
145	VI-43		
146	VI-44		
147	VI-48	891	626
148	VI-49	-	-
149	VI-50	893	585
150	VI-52	-	
151	VI-53	895	560
152	VI-55	897	509
153	VI-65	-	-
154	VI-70	108	550
155	VI-71		
133	V 1-7 1	لـــــا	

156	VI-72		-
157	VI-74	905	655
158	VI-76	907	582
159	VI-78	<u> </u>	<u> </u>
160 .	VI-79		-
161	VI-84		•
162	VI-87	911	595
163	VI-88	912	651
164	VI-90	-	-
165	VI-93	-	-
166	VI-95	915	230
167	VI-96	-	-
168	VII-02	-	
169	VII-03	1196	412
170	VII-06	-	
171	VII-10		-
172	VII-11	-	-
173	VII-15	1199	439
174	VII-19	562	580
175	VII-21	564	671
176	VII-25	-	-
177	VII-32	571	457
178	VII-36	575	209
179	VII-39	576	541
180	VII-42	579	502
181	VII-43	580	316
182	VII-46	583	631
183	VII-47	1200	526
184	VII-48	1201	613
185	VII-59	593	565
186	VII-60	-	•
187	VII-63	595	98
188	VII-66	598	362
189	VII-67	-	-
190	VII-72	600	595
191	VII-73	601	522
192	VII-75	•	-
193	VII-76	603	624
194	VII-77	1203	692
195	VII-80	605	338
196	VII-81	606 .	556
197	VII-83		
198	VII-86	-	-
199	VII-88	•	-
200	VII-90	612	576
201	VII-91	613	341
202	VII-93	615	379
203	VIII-01		-
204	VIII-02		
205	VIII-03	-	-
206	VIII-06	-	
207	VIII-09	618	598
208	VIII-10	-	-
209	VIII-15		
210	VIII-20	628	419
211	VIII-22		
<u></u>			

			. 76
	VIII OC		
212	VIII-26	- CO4	
213	VIII-28	634	511
214	VIII-29	635	592
215	VIII-30	636	572
216	VIII-31	637	482
217	VIII-32	638	545
218	VIII-33	639	624
219	VIII-39		640
220	VIII-41	645 646	649
221	VIII-42 VIII-44	040	600
222		640	405
223	VIII-46	649	425
224	VIII-48	651	251
225	VIII-58		
226	VIII-64	663	627
227	VIII-65	205	
228	VIII-66	665	345
229	VIII-67	666	252
230	VIII-74		504
231	VIII-76	675	591
232	VIII-78		
233	VIII-82		
234	VIII-83		
235	VIII-85		
236	VIII-87		
237	VIII-91		
238	VIII-92		
239	VIII-93		
240	VIII-95		•
241	X-04		641
242	X-07	808	132
243	X-15	814 821	370
244	X-29		3/0
245	X-34		
246	X-35	207	COO
247	X-54	837	603
248	X-56	839	71
249	X-68	1207	642
250	X-72	849	622
251	X-94	860	501
252	XI-07		000
253	XI-13	1209	620
254	XI-50		
255	XI-58		674
256	XI-81	1212	374
257	XII-07	1213	567
258	XII-17		
259	XII-26	-	
260	XII-27		
261	XII-31		
262	XII-32		
263	XII-35	1214	620
264	XII-36	-	•
265	XII-52		•
266	XII-59	1216	484
267	XIII-19	1219	559

268	XIII-29	-	-
269	XIII-52	939	513
270	XIII-62	-	-
271	XIII-84	•	-
272	XIII-92	1221	741
273	XV-18	-	•
274	XV-22	1099	561
275	XV-24	-	-
276	XV-25	1224	485
277	XV-28	-	-
278	XV-34	-	•
279	XV-42	٠	-
280	XV-68	-	-
281	XV-74	·	-
282	XV-93	-	•
283	XV-94	-	-
284	XV-96	-	-
285	XVI-36	1056	435
286	XVI-53	1230	741
287	XVI-59	-	-
288	XVI-66	1074	689
289	XVI-76	1083	198
290	XVI-77	1084	198
291	XVII-07	-	
292	XVII-08	-	
293	XVII-17	-	-
294	XVII-28	•	
295	XVII-29	-	•
296	XVII-31	1139	503
297	XVII-36	•	
298	XVII-39	•	-
299	XVII-40	1231	203
300	XVII-48	1148	587
301	XVII-55	-	•
302	XVII-58	-	•
303	XVII-67	-	-
304	XVII-72		
305	XVII-76	1160	650
306	XVII-82	•	
307	XVII-87	1165	502
308	XVII-95	1172	648

Table 1 b

List of sequences of probes informative for disease diagnosis

Please see the note at the bottom

Clone ID	Sequence ID
1-09	298
	299
I-10	
1-13	1331
I-14	1178
I-15	300
1-16	301
I-17	302
I-19	304
1-20	305
1-22	306
I-23	307
1-24	308
1-25	309
I-28	310
1-30	1180
1-31	311
1-32	312
1-34	313
1-37	1440
1-38	314
1-39	315
1-40	316
1-40	1332
	317
1-44	
1-45	318
1-46	319
1-47	320
1-48	321
I-49	322
I-53	323
1-54	1181
I-56	324
I-57	325
1-58	326
1-60	327
1-64	328
I-67	330
1-69	331
I-71	332
1-72	333
1-73	334
177	
1-77	335
I-79	336
I-80	337

1-81	338
I-82	339
I-86	1336
I-88	1182
1-95	1337
11-02	360
11-03	361
11-05	363
11-06	364
11-07	365
11-08	366
11-09	367
II-10	368
11-11	369
11-12	370
II-13	371
11-14	372
II-15	373
11-16	374
II-17	375
II-18	376
11-20	377
II-21	378
11-22	379
11-23	380
11-24	381
11-25	382
11-26	383
11-27	384
11-28	385
11-29	386
11-30	387
11-31	388
II-32	389
11-33	390
11-34	391
11-35	392
11-37	393
11-38	394
11-39	395
II-40	396
II-41	397
11-42	398
11-43	399
11-43	400
II-46	401
11-47	401
II-4 <i>1</i>	402
II-49	403
II-49 II-50	404
11-50	405
11-52	1 400

11-53	407
11-54	408
11-55	409
11-56	410
11-57	411
11-58	412
11-59	413
11-60	414
II-61	415
11-62	416
11-63	417
11-64	418
11-65	419
11-66	420
11-67	421
11-68	422
11-69	423
11-70	424
11-71	425
II-72	426
11-73	427
11-74	428
11-75	429
11-76	430
11-77	431
11-78	432
11-79	433
11-80	434
II-81	435
II-82	436
11-83	437
11-84	438
11-85	439
11-86	440
11-87	441
11-88	442
11-89	443
11-90	444
11-91	445
11-92	446
II-93	447
11-94	448
11-95	449
11-96	450
III-01	452
111-02	453
111-03	454
III-04	455
111-05	457
111-06	458
111-07	459
	J

111-08	460
111-09	461
111-11	462
III-12	463
III-13	464
111-14	465
111-15	466
III-16	467
III-17	468
III-18	469
III-19	470
111-20	1183
111-21	471
111-22	472
111-23	473
111-24	474
111-25	475
III-26	476
111-27	477
111-28	478
111-29	479
III-31	481
111-32	482
111-33	483
111-34	484
111-35	485
111-37	486
111-39	487
111-40	488
111-42	489
111-43	490
iii-44	491
111-45	492
111-46	493
111-47	494
III-48	495
111-49	496
111-50	497
III-51	498
III-52	499
111-53	500
111-54	501
111-55	. 502
III-56	503
111-57	504
111-58	505
III-59	506
111-61	507
111-62	508
III-63	509
111-64	. 510

III-65	511
111-66	512
111-67	513
III-69	514
111-70	515
111-71	516
111-73	517
111-74	518
111-75	519
111-77	520
III-78	521
111-79	522
111-80	523
111-81	524
III-82	1348
111-83	525
111-85	526
III-86	527
111-87	528
111-88	529
111-89	530
III-91	531
111-92	1351
111-93	532
111-94	533
111-95	534
111-96	535
IV-02	681
IV-04	682
IV-13	683
IV-14	684
IV-15	1185
IV-17	685
IV-23	1353
IV-26	1186
IV-28	686
IV-31	687
IV-32	688
IV-35	1355
IV-37	g6
IV-38	689
IV-40	690
IV-42	691
IV-43	1239
IV-44	692
IV-47	693
IV-53	61
IV-55	694
IV-56	695
IV-61	696
IV-64	697
	1

IV-65	698
IV-69	192
IV-72	699
IV-73	700
IV-80	701
IV-82	196
IV-85	702
IV-93	703
IV-95	704
IV-96	705
IX-10	736
IX-12	738
IX-13	739
IX-24	747
IX-38	757
IX-39	758
IX-48	764
IX-50	766
IX-56	768
IX-62	773
IX-65	776
IX-72	782
IX-72	785
IX-77	783
IX-96	801
V-01	1361
V-01	706
V-04	707
V-07	708
V-07	709
V-09	710
V-11	1188
V1-16	873
V1-10 V1-19	875
V-12	711
V-12 V-17	1364
V-17 V-18	712
V-10 V-20	713
V-24	713
V-24 V-25	
	1365 1189
V-28	
V-35	1366
V-37	716
V-38	1190
V-39	1109
V-40	717
V-41	718
V-47	1368
V-48	719
V-49	1369
V-55	77

p	
V-57	720
V-58	1370
V-61	721
V-64	722
V-65	723
V-68	1448
V-71	1495
V-74	724
V-75	1372
V-80	726
V-81	727
V-87	728
V-90	1374
VI-02	340
VI-03	341
VI-04	342
VI-06	343
VI-07	344
VI-08	345
VI-09	346
VI-11	347
VI-12	869
VI-13	870
VI-14	871
VI-16	873
VI-18	348
VI-19	349
VI-20	350
VI-21	351
VI-22	352
VI-22	878
VI-23	879
VI-25	353
VI-25	354
VI-20	355
VI-27	355
VI-32	885
VI-33	357
VI-35	358
VI-39	887
VI-43	1382
VI-44	1193
VI-45	889
VI-48	359
VI-49	892
VI-50	893
VI-53	895
VI-55	897
VI-58	899
VI-66	903
VI-67	904

VI-71         1387           VI-74         905           VI-75         906           VI-76         907           VI-77         110           VI-80         908           VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-93         1391           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-18         561           VII-19         562           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566 <th>(</th> <th></th>	(	
VI-71         1387           VI-74         905           VI-75         906           VI-77         110           VI-79         1389           VI-80         908           VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-93         1391           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-08         553           VII-09         554           VII-09         554           VII-09         554           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         563	VI-70	108
VI-74         905           VI-75         906           VI-76         907           VI-77         110           VI-80         908           VI-85         910           VI-85         911           VI-87         911           VI-88         912           VI-90         1390           VI-93         1391           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558 <t< td=""><td></td><td>1387</td></t<>		1387
VI-75         906           VI-76         907           VI-77         110           VI-80         908           VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-13         558           VII-14         558           VII-15         559           VII-16         557           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566		
VI-76         907           VI-77         110           VI-80         908           VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-93         1391           VI-95         915           VII-96         1392           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-13         558           VII-14         558           VII-15         559           VII-16         559           VII-17         560           VII-18         561           VII-19         562           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566		
VI-77         110           VI-79         1389           VI-80         908           VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-13         556           VII-14         558           VII-15         559           VII-16         551           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567		
VI-79         1389           VI-80         908           VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-93         1391           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-16         561           VII-17         560           VII-18         561           VII-29         565		
VI-80         908           VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-93         1391           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-16         559           VII-17         560           VII-18         561           VII-19         562           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-28         569		
VI-85         910           VI-87         911           VI-88         912           VI-90         1390           VI-93         1391           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-14         558           VII-17         560           VII-18         561           VII-19         562           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-28         569		<del></del>
VI-87       911         VI-88       912         VI-90       1390         VI-93       1391         VI-95       915         VI-96       1392         VII-02       547         VII-03       548         VII-04       549         VII-05       550         VII-06       551         VII-07       552         VII-08       553         VII-09       554         VII-10       555         VII-11       556         VII-12       557         VII-14       558         VII-15       559         VII-16       561         VII-17       560         VII-18       561         VII-19       562         VII-19       562         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-29       570         VII-31       570         VII-32       571         VII-33       572 </td <td></td> <td></td>		
VI-88       912         VI-90       1390         VI-93       1391         VI-95       915         VI-96       1392         VII-02       547         VII-03       548         VII-04       549         VII-05       550         VII-06       551         VII-07       552         VII-08       553         VII-09       554         VII-10       555         VII-11       556         VII-12       557         VII-14       558         VII-15       559         VII-17       560         VII-18       561         VII-19       562         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-29       570         VII-32       571         VII-34       573         VII-35       574         VII-36       575         VII-39       576     <		
VI-90         1390           VI-93         1391           VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-34         573           VII-35         574           VII-36         575 </td <td></td> <td></td>		
VI-93       1391         VI-96       1392         VII-02       547         VII-03       548         VII-04       549         VII-05       550         VII-06       551         VII-07       552         VII-08       553         VII-09       554         VII-10       555         VII-11       556         VII-12       557         VII-14       558         VII-15       559         VII-17       560         VII-18       561         VII-19       562         VII-19       562         VII-20       563         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577		
VI-95         915           VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577 </td <td></td> <td></td>		
VI-96         1392           VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-16         561           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-34         573           VII-35         574           VII-36         575           VII-37         576           VII-39         576     <		l
VII-02         547           VII-03         548           VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-39         570           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578     <		
VII-03       548         VII-04       549         VII-05       550         VII-06       551         VII-07       552         VII-08       553         VII-09       554         VII-10       555         VII-11       556         VII-12       557         VII-14       558         VII-15       559         VII-17       560         VII-18       561         VII-19       562         VII-20       563         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-39       570         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-04         549           VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579		
VII-05         550           VII-06         551           VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-39         576           VII-40         577           VII-41         578           VII-42         579		
VII-06         551           VII-07         552           VII-08         553           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-29         570           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579		
VII-07         552           VII-08         553           VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         569           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-29         570           VII-33         572           VII-34         573           VII-35         574           VII-39         576           VII-40         577           VII-41         578           VII-42         579		<u></u>
VII-08       553         VII-10       555         VII-11       556         VII-12       557         VII-14       558         VII-15       559         VII-17       560         VII-18       561         VII-19       562         VII-20       563         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-09         554           VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-32         570           VII-33         572           VII-34         573           VII-35         574           VII-39         576           VII-40         577           VII-41         578           VII-42         579		<u></u>
VII-10         555           VII-11         556           VII-12         557           VII-14         558           VII-15         569           VII-17         560           VII-18         561           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-39         576           VII-40         577           VII-41         578           VII-42         579		·
VII-11         556           VII-12         557           VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-34         573           VII-35         574           VII-36         575           VII-40         577           VII-41         578           VII-42         579		
VII-12         557           VII-14         558           VII-15         569           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-29         570           VII-33         572           VII-34         573           VII-35         574           VII-39         576           VII-40         577           VII-41         578           VII-42         579		
VII-14         558           VII-15         559           VII-17         560           VII-18         561           VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-29         570           VII-33         572           VII-34         573           VII-35         574           VII-39         576           VII-40         577           VII-41         578           VII-42         579	VII-11	
VII-15       559         VII-17       560         VII-18       561         VII-19       562         VII-20       563         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-12	557
VII-17       560         VII-18       561         VII-19       562         VII-20       563         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-14	558
VII-18       561         VII-19       562         VII-20       563         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-31       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-15	559
VII-19       562         VII-20       563         VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-17	560
VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-25         1397           VII-26         250           VII-27         568           VII-28         569           VII-29         570           VII-33         572           VII-34         573           VII-35         574           VII-39         576           VII-40         577           VII-41         578           VII-42         579	VII-18	561
VII-21       564         VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-19	562
VII-22       565         VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-20	563
VII-23       566         VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-21	564
VII-24       567         VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-22	565
VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-23	566
VII-25       1397         VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579	VII-24	567
VII-26       250         VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		1397
VII-27       568         VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		250
VII-28       569         VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-29       570         VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-32       571         VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-33       572         VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-34       573         VII-35       574         VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-35     574       VII-36     575       VII-39     576       VII-40     577       VII-41     578       VII-42     579		
VII-36       575         VII-39       576         VII-40       577         VII-41       578         VII-42       579		1
VII-39       576         VII-40       577         VII-41       578         VII-42       579		
VII-40       577         VII-41       578         VII-42       579		
VII-41 578 VII-42 579		
VII-42 579		
VII-43 . 300		
	V11-43	. 300

VII-44	581
VII-45	582
VII-46	583
VII-47	1200
VII-48	584
VII-49	. 585
VII-50	586
VII-52	587
VII-53	588
VII-54	589
VII-55	· 590
VII-57	591
VII-58	592
VII-59	593
VII-62	594
VII-63	595
VII-64	596
VII-65	597
VII-66	598
VII-67	1399
VII-71	599
VII-72	600
VII-73	601
VII-74	602
VII-76	603
VII-77	604
VII-80	605
VII-81	606
VII-82	607
VII-83	608
VII-84	609
VII-86	1453
VII-87	610
VII-89	611
VII-90	612
VII-91	613
VII-92	614
VII-93	615
VII-94	616
VII-96	617
VIII-09	618
VIII-10	619
VIII-11	620
VIII-12	621
VIII-13	622
VIII-15	623
VIII-15	624
VIII-17	625
VIII-18	626
VIII-18	627
VIII-19 VIII-20	628
V111-20	1020

VIII-21	629
VIII-22	1455
VIII-23	630
VIII-24	631
VIII-25	632
VIII-26	1456
VIII-27	633
VIII-28	634
VIII-29	635
VIII-30	636
VIII-31	637
VIII-32	638
VIII-33	639
VIII-34	640
VIII-36	641
VIII-37	642
VIII-38	643
VIII-40	644
VIII-41	645
VIII-42	646
VIII-43	647
VIII-45	648
VIII-46	649
VIII-47	650
VIII-48	651
VIII-50	652
VIII-51	653
VIII-53	654
VIII-54	655
VIII-55	. 656
VIII-56	657
VIII-57	658
VIII-58	659
VIII-59	660
VIII-60	661
VIII-61	662
VIII-64	663
VIII-65	664
VIII-66	665
VIII-67	666
VIII-68	667
VIII-69	668
VIII-70	669
VIII-71	670
VIII-72	671
VIII-73	672
VIII-74	673
VIII-75	674
VIII-76	675
VIII-77	676
VIII-78	677

VIII-79	678
VIII-80	679
X-07	808
X-15	814
X-20	817
X-29	821
X-34	825
X-46	833
X-54	837
X-56	839
X-68	1207
X-72	849
X-73	1208
X-94	860
XI-13	1209
XI-37	1460
VI 42	1210
XI-43 XI-67	1211
XI-81	1212
XII-07	1213
XII-35	1214
VII 26	1215
XII-59	1216
XII-65	1028
XII-92	1217
XIII-03	917
XIII-04	1218
XIII-19	1219
XIII-24	926
XIII-51	938
XIII-51	939
XIII-67	947
XIII-69	947
XIII-88	1220
XIII-92	1221
XV-22	1099
XV-24 XV-25	1101 1224
XV-42	
XV-42 XV-62	1108
XV-62 XV-64	1226
	1118
XV-84	1125
XVI-19	1228
XVI-36	1056
XVI-53	1230
XVI-60	1071
XVI-66	1074
XVI-74	1081
XVI-76	1083
XVI-77	1084
XVII-31	. 1139

XVII-40	1231
XVII-48	1148
XVII-76	1160
XVII-87	1165
XVII-95	1172

#### Note

Sequences not available for sequence IDs in Table 1, and corresponding sequence Ids in Table 2 and 4.

298,301,305,307,312,317,318,319,320,332,333,334,336,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,367,372,375,376,377,379,385,392,393,404,437,439,440,443,444,445,449,455,457,465,466,467,468,470,486,498,501,511,514,516,517,520,522,528,531,535,547,548,549,550,551,552,553,554,555,556,557,558,559,573,584,604,608,616,620,623,640,659,662,664,667,668,673,677,678,679,681,695,702,712,716,825,886,894,902,909,916,1101,1108,1109,1177,1187,1193,1204,1220,1239,1255,1256,1342,1347,1354,1357,1362,1363,1364,1373,1375,1379,1403,1404,1405,1406,1413

Table 2a
List of informative probes for diagnosis of breast cancer

Clone ID	Sequence ID
1-24	308
1-28	310
1-30	1180
1-52	-
1-54	1181
11-41	397
11-70	424
11-87	441
III-06	458
111-20	1183
111-40	488
111-57	504
111-60	-
lii-61	507
111-89	530
IV-14	684
IV-15	1185
IV-26	1186
IV-32	688
IV-41	-
IV-53	61
IV-62	-
IV-69	192
IV-80	701
IV-82	196
IX-10	736
IX-12	-
IX-38	757
IX-39	758
IX-42	•
IX-48	764
IX-77	785
	1188
V-11 V-32	
V-39	_
V-55	77
V-80	726
V-94	
VI-07	93
VI-34	
VI-41	
VI-48	891
VI-49	
VI-52	
VI-55	897
VI-65	<u> </u>
VI-65 VI-70	108
VI-70	מטו

Clone ID	Sequence ID
VI-72	-
VI-78	
VI-84	
VII-03	1196
VII-15	1199
VII-32	
	571
VII-39	576
VII-47	1200
VII-48	1201
VII-60	
VII-73	601
VII-77	1203
VII-90	612
VIII-20	628
VIII-29	635
VIII-30	636
VIII-31	637
VIII-39	
VIII-44	-
VIII-46	649
VIII-48	651
VIII-66	665
VIII-74	_
VIII-76	675
X-04	
X-07	808
X-15	814
X-29	821
X-34	
X-35	
X-54	837
	839
X-56	
X-68	1207
X-72	849
X-94	860
XI-07	<u> </u>
XI-13	1209
XI-50	
XI-58	-
XI-81	1212
XII-07	1213
XII-17	•
XII-26	•
XII-27	·
XII-31	_
XII-32	
XII-35	1214
VII-22	1614

Clone ID	Sequence ID
XII-36	Ocquerice ib
XII-52	
XII-59	1216
XIII-19	1219
XIII-19 XIII-29	1213
XIII-52	939
XIII-62	939
XIII-84	<del></del>
XIII-92	4004
XV-18	1221
XV-22	4000
	1099
XV-24	4004
XV-25	1224
XV-28	
XV-34	`-
XV-42	
XV-68	
XV-74	
XV-93	~
XV-94	
XV-96	
XVI-36	1056
XVI-53	1230
XVI-59	
XVI-66	1074
XVI-76	1083
XVI-77	1084
XVII-07	-
XVII-08	
XVII-17	·
XVII-28	
XVII-29	
XVII-31	1139
XVII-36	-
XVII-39	
XVII-40	1231
XVII-48	1148
XVII-55	
XVII-58	
XVII-67	-
XVII-72	-
XVII-76	1160
XVII-82	•
XVII-87	1165
XVII-95	1172

Table 2b

### List of sequences of probes informative for breast cancer

Please see the note at the bottom of Table 1. Some sequences are missing.

Clone ID	Sequence ID
1-13	1331
1-14	1178
1-24	308
I-25	309
1-28	310
1-30	1180
1-37	1440
I-42	1332
1-48	321
1-54	1181
I-60	327
1-72	1335
1-81	338
1-82	339
1-86	1336
1-88	1182
1-95	1337
II-02	360
11-03	361
11-06	364
11-07	365
11-10	368
11-21	378
11-23	380
II-24	381
11-25	382
11-27	384
II-33	390
11-34	391
11-41	397
11-42	398
11-46	401
11-47	1338
11-48	403
11-52	406
11-57	411
11-58	412
11-59	413
11-60	414
11-61	415
11-62	416
11-64	418

11-67	421
11-69	
	423
11-70	424
11-74	428
II-80	434
11-82	436
11-84	438
11-87	441
11-88	442
11-96	450
III-01	452
111-02	453
111-06	458
111-08	460
111-12	463
III-13	464
111-17	1344
111-18	469
III-20	1183
III-21	471
111-23	473
111-24	474
III-25	475
III-26	476
111-27	477
III-28	478
III-29	479
III-32	482
111-33	483
III-35	485
III-39	487
111-40	488
III-42	489
111-42	492
111-46	493
111-47	494
III-48	495
111-56	503
111-57	504
-58	505
III-59	506
III-61	507
111-62	508
111-63	509
III-64	510
III-66	512
III-67	513
111-70	515
111-74	518
III-75	519
111-78	521

III-80	523
III-80	523
III-82	1348
<del></del>	
111-85	526
III-86	527
111-88	529
111-89	530
III-92	1351
III-93	532
III-95	534
111-96	1352
IV-04	682
IV-13	683
IV-14	684
IV-15	1185
IV-17	685
IV-23	1353
IV-26	1186
IV-31	687
IV-32	688
IV-35	1355
IV-37	g6
IV-38	689
IV-42	691
IV-43	1239
IV-47	693
IV-53	61
IV-61	696
IV-64	697
IV-69	192
IV-72	699
IV-80	701
IV-82	196
IV-85	702
IV-93	1360
IV-96	705
	736
IX-10	738
IX-12	739
IX-13	
IX-24	747
IX-38	757
IX-39	758
IX-48	764
IX-50	766
IX-56	768
IX-62	773
IX-65	776
IX-72	782
IX-77	785
IX-91	796
IX-96	801
<del></del>	

V-01	1361
V-03	706
V-04	707
V-07	708
V-08	709
V-11	.1188
V-12	711
V-17	1364
V-24	714
V-25	1365
V-28	1189
V-35	1366
V-38	1190
V-39	1109
V-41	718
V-47	1368
V-49	1369
V-55	77
V-57	720
V-58	1370
V-61	721
V-64	722
V-65	1371
V-68	1448
V-71	1495
V-74	724
V-75	1372
V-80	726
V-90	1374
VI-03	864
VI-04	865
VI-07	93
VI-08	867
VI-09	1378
VI-12	869
VI-13	870
VI-14	871
VI-16	873
VI-19	875
VI-20	876
VI-21	1380
VI-23	878
VI-24	879
VI-25	1192
VI-26	881
VI-32	885
VI-39	887
VI-43	1382
VI-44	1193
VI-45	889 .
VI-48	891

VI-49	892
VI-50	893
VI-53	895
VI-55	897
VI-58	899
VI-66 .	903
VI-67	904
VI-70	108
VI-71	1387
VI-74	905
VI-75	906
VI-76	907
VI-77	110
VI-79	1389
VI-80	908
VI-85	910
VI-87	911
VI-88	912
VI-90	1390
VI-93	1390
VI-95	915
VI-96	1392
VII-02	1195
VII-02	1195
VII-06	
VII-08	1394 1197
VII-09	1198
VII-10	1395
VII-11	1396
VII-15	1199
VII-17	560
VII-19	562
VII-21	564
VII-22	565
VII-23	566
VII-24	567
VII-25	1397
VII-26	250
VII-27	568
VII-29	570
VII-32	571
VII-33	572
VII-36	575
VII-39	576
VII-41	578
VII-42	579
VII-43	580
VII-46	583
VII-47	1200
VII-48	1201
VII-49	585
· · · · · · · · · · · · · · · · · · ·	

VIII E 4	589
VII-54 VII-57	591
	592
VII-58	593
VII-59	594
VII-62	1202
VII-63	
VII-64	596
VII-66	598 1399
VII-67	600
VII-72	601
VII-73	1203
VII-77	
VII-80	605
VII-82	607
VII-86	1453
VII-87	610
VII-90	612
VII-91	613
VII-92	614
VII-93	615
VII-96	617
VIII-09	618
VIII-10	619
VIII-13	622
VIII-16	624
VIII-20	628
VIII-21	629
VIII-22	1455
VIII-23	630
VIII-24	631
VIII-25	632
VIII-26	1456
VIII-27	633
VIII-28	634
VIII-29	635
VIII-30	636
VIII-31	637
VIII-32	638
VIII-33	639
VIII-34	1204
VIII-38	643
VIII-40	644
VIII-41	645
VIII-46	649
VIII-48	651
VIII-55	656
VIII-57	658
VIII-59	660
VIII-60	661
VIII-61	1205
VIII-64	. 663
<u> </u>	

VIII-66	665
VIII-73	672
VIII-74	673
VIII-76	675
VIII-80	679
X-07	808
X-15	814
X-20	817
X-29	821
X-34	825
X-46	833
X-54	837
X-56	839
X-68	1207
X-72	849
X-73	1208
X-94	860
XI-13	1209
XI-37	1460
XI-43	1210
XI-67	1211
XI-81	1212
XII-07	1213
XII-35	1214
XII-36	1215
XII-59	1216
XII-65	1028
XII-92	1217
XIII-03	917
XIII-04	1218
XIII-19	1219
XIII-24	926
XIII-51	938
XIII-52	939
XIII-67	947
XIII-69	949
XIII-88	1220
XIII-92	1221
XV-22	1099
XV-24	1101
XV-25	1224
XV-42	1108
XV-62	1226
XV-64	1118
XV-84	1125
XVI-19	1228
XVI-36	1056
XVI-53	1230
XVI-60	1071
XVI-66	1074
XVI-74	1081

XVI-76	1083
XVI-77	1084
XVII-31	1139
XVII-40	1231
XVII-48	1148
XVII-76	1160
XVII-87	1165
XVII-95	1172

## Table 3

List of informative probes (Clone ID) selected for breast cancer diagnosis based on their occurrence criterion during variable selection

Occurrence*	Clone ID
100%	XI-8,XVI-66,VM-66,XVI-59,VII-03,XIII-19,XII-35,X-35,XI-
	50,XII-26,IV-53,XIII-29,XIII-62,I-30,III-06,XV-22,XV-94,VII-
	15,VII-39,IX-39,XVII-39,III-40,VII-32
90%	1-52,VI-65,VI-34,IV-62,XV-34,XVII-58,V-11,VI-78,XII-36,XIII-
	92,VIII-29,XVI-53,XVI-77,XI-13,XIII-84,IV-14,XII-31,V-80,VII-
•	48,XVII-29,XVII-72
80%	111-60,VIII-74,IX-12,X-04,XIII-52,VM-30,IX-38
70%	VI-49,X-29,VIII-48
60%	IV-82,IX-10,VI-52,X-68,VII-77
50%	IV-15
40%	XV-28,11-70,V-55
30%	XVII-17,XVII-67
20%	XI-58,XVI-36,VIII-39,VIII-44,III-61,IV-69,XV-68,X-72
10%	IX-42,IX-77,X-94,XV-96,XVIJ-55
5%	XII-59,XVI-76,I-54,XV-18,V-94,X-54,VI-07,VII-47,XVII-
	31,XVII-87,XVII-48
In at least one model	II-41,VI-41,III-57,III-89,VII-73,XV-25,IV-26,X-34,IV-41,VII-
	90,XV-42,XVII-82,XII-27,VIII-20,I-28,VII-60,VIII-76,III-20,VI-
•	84,XI-07,XVII-28,XII-17,XVII-36,XII-52 ,XVII-76,VIII-46,VI-
•	70,XV-74,XV-93,VIII-31,II-87,V-39 ,VI-55,X-07,X-15,XII-
	07,XVII-07,XVII-08,XVII-95,I-24,IV-32,V-32,VI-48,VI-72,IV-
	80,IX-48,X-56,XV-24,XII-32,XVII-40

<sup>\*100% =</sup> Genes appearing in all the 75 cross validated models; 90% = Additional genes appearing in at least 68 out of 75 cross validated models; 5% = Additional genes appearing in at least 4 out of 75 cross validated models and so on.

Table 4q

# List of informative probes for diagnosis of Alzheimer disease

Clone ID	Sequence ID
1-01	-
1-02	-
I-13	
I-21	•
1-34	313
1-37	
1-42	-
I-58	326
1-71	<del>-</del>
1-72	-
1-86	•
1-95	-
11-03	361
11-05	363
11-06	364
11-10	368
11-24	381
11-25	382
11-26	383
11-33	390
11-34	391
11-42	398
11-47	•
11-57	411
11-61	415
11-69	423
11-75	429
11-83	•
11-84	438
11-88	442
11-90	
II-94	448
111-02	453
111-05	-
111-06	458
111-08	460
111-10	
III-13	464
III-15	
111-17	
111-23	473
111-26	476
111-35	485
111-39	487
111-43	490
111-44	491
111-53	
111-55	500
111-20	503

Clone ID	Sequence ID
111-60	Sequence in
111-63	F60
	509
111-68	
111-74	518
08-111	523
III-82	-
III-85	526
111-92	-
- <del>9</del> 6	-
IV-23	
IV-26	-
IV-29	-
IV-31	687
IV-34	•
IV-35	
IV-45	·
IV-80	701
IV-82	_
IV-93	
V-01	
V-02	
V-03	706
V-04	707
V-06	
V-07	708
V-12	717
V-15	
V-17	
V-21	
V-25	
V-25 V-35	
V-42 V-43	
V-47	
V-49	
V-52	-
V-54	•
V-58	<u>-</u>
V-59	•
V-65	•
V-68	-
V-71	-
V-75	
V-79	
V-80	726
V-90	
V-90 V-91	
V-92	
N-25	

-		`	
- 1	•	12	

Clone ID	Sequence ID
VI-02	•
VI-04	865
VI-09	
VI-10	
VI-12	000
	869
VI-14	871
VI-17	
VI-20	876
VI-21	-
VI-23	878
VI-41	
VI-42	
VI-43	<del></del>
VI-44	-
VI-48	891
VI-49	•
VI-50	893
VI-53	895
VI-71	
	-
VI-74	905
VI-76	907
VI-78	
VI-79	-
VI-87	911
VI-88	912
VI-90	
VI-93	
VI-95	
	915
VI-96	
VII-02	•
VII-03	_
VII-06	-
VII-10	-
VII-11	
VII-19	562
VII-21	564
VII-25	•
VII-36	575
VII-42	579
VII-43	580
VII-46	583
VII-59	
	593
VII-63	595
VII-66	598
VII-67	
VII-72	600
VII-73	601
VII-75	
VI-02	
VI-04	866
VI-09	•
VI-10	-
VI-12	873
VI-14	875
VI-17	0/3
VI-1/	
_	

Clone ID	Sequence ID
VII-91	613
VII-93	615
VIII-01	-
VIII-02	-
VIII-03	-
VIII-06	-
VIII-09	618
VIII-10	-
VIII-15	-
VIII-22	-
VIII-26	-
VIII-28	634
VIII-30	636
VIII-32	638
VIII-33	639
VIII-41	645
VIII-42	646
VIII-48	651
VIII-58	•
VIII-64	663
VIII-65	
VIII-67	666
VIII-78	
VIII-82	-
VIII-B3	
VIII-85	-
VIII-87	-
VIII-91	-
VIII-92	-
VIII-93	-
VIII-95	-

Table 4 b

### List of sequences of probes informative for Alzheimer disease

Please see note to Table 1

<u> </u>	
Clone ID	Sequence ID
1-09	298
1-10	299
I-15	300
I-16	301 .
I-17	302
I-19	304
1-20	305
1-22	306
I-23	307
1-24	308
1-25	309
I-28	310
1-31	311
1-32	312
1-34	313
1-38	314
1-39	315
1-40	316
1-44	317
1-45	318
1-46	319
1-47	320
I-48	321
1-49	322
1-53	323
1-56	324
1-57	325
1-58	326
1-60	327
1-64	328
1-67	330
1-69	331
1-71	332
1-72	333
1-73	334
1-77	335
1-79	336
1-80	337
I-81	338
I-82	339
VI-02	340
V. 02	

1 100	341
VI-03	342
VI-04	343
VI-06	
VI-07	344
VI-08	345
VI-09	346
VI-11	347
VI-18	348
VI-19	349
VI-20	350
VI-21	351
VI-22	352
VI-25	353
VI-26	354
VI-27	355
VI-31	356
VI-33	357
VI-35	358
VI-48	359
11-02	360
11-03	361
11-05	363
11-06	364
11-07	365
11-08	366
11-09	367
II-10	368
11-11	369
II-12	370
II-13	371
11-14	372
11-15	373
II-16	374
11-17	375
11-17	376
	377
11-20	<del></del>
II-21	378
11-22	379
11-23	380
11-24	381
11-25	382
11-26	383
11-27	384
11-28	385
11-29	386
11-30	387
II-31	388
II-32	389
11-33	390
11-34	391
II-35	392

11-37	393
II-38	394
11-39	395
11-40	396
11-40	397
11-41	398
11-42	399
	400
11-44	400
11-46	401
11-47	402
11-48	
11-49	404
11-50	405
11-52	406
II-53	407
11-54	408
11-55	409
11-56	410
11-57	411
11-58	412
11-59	413
11-60	414
11-61	415
11-62	416
11-63	417
11-64	418
11-65	419
11-66	420
11-67	421
11-68	422
11-69	423
11-70	424
11-71	425
11-72	426
11-73	427
11-74	428
11-75	429
11-76	430
11-77	431
11-78	432
11-79	433
11-80	434
II-81	435
11-82	436
11-83	437
11-84	438
11-85	439
11-86	440
11-87	441
11-88	442
11-89	443

111-90	444
II-91	445
11-92	446
11-93	447
11-94	448
11-95	449
11-96	450
III-01	452
111-02	453
111-03	454
111-04	455
III-05	457
111-06	458
111-07	459
111-08	460
111-09	461
111-03	462
111-11	463
III-12 III-13	464
111-13	465
	466
111-15	467
III-16	468
111-17	469
111-18	
111-19	470
III-21	471
111-22	472
III-23	473
111-24	474 475
III-25 III-26	
111-26	476 477
111-27	477
	479
111-29	481
III-31	
III-32	482
111-33	483
111-34	484
111-35	485
111-37	486
111-39	487
111-40	488
111-42	489
111-43	. 490
111-44	491
111-45	492
111-46	493
111-47	494
111-48	495
111-49	496
111-50	497

III-51	498
III-52	499
111-53	500
111-54	501
III-55	502
111-56	503
111-57	504
111-58	505
111-59	506
III-61	507
111-62	508
III-63	509
III-64	510
111-65	511
111-66	512
III-67	513
111-69	514
111-70	515
III-70	516
111-73	517
111-73	518
111-75	519
111-75	520
111-77	520
111-78	522
	522
III-80	523 524
III-81	524 525
111-83	
111-85	526 527
111-86	527
111-87	528 529
111-88	529
111-89	530
111-91	531
111-93	532
111-94	533
III-95	534
111-96	535
VII-02	547
VII-03	548
VII-04	549
VII-05	550
VII-06	551
VII-07	552
VII-08	553
VII-09	554
VII-10	555
VII-11	556
VII-12	557
VII-14	558
VII-15	559
L	

VII-17         560           VII-18         561           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-59         593 </th <th>VII-17</th> <th>500</th>	VII-17	500
VII-19         562           VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-24         567           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-59         593 </td <td></td> <td>560</td>		560
VII-20         563           VII-21         564           VII-22         565           VII-23         566           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-59         593           VII-61         596 </td <td></td> <td><del> </del></td>		<del> </del>
VII-21         564           VII-23         565           VII-24         567           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-50         586           VII-51         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-58         592           VII-59         593           VII-61         596 </td <td></td> <td><del> </del></td>		<del> </del>
VII-22         565           VII-23         566           VII-24         567           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-61         598           VII-62         594 </td <td></td> <td><del></del></td>		<del></del>
VII-23         566           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-71         599           VII-72         600 </td <td></td> <td></td>		
VII-24         567           VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596 </td <td></td> <td><del></del></td>		<del></del>
VII-27         568           VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-71         599 </td <td></td> <td>566</td>		566
VII-28         569           VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-71         599           VII-72         600 </td <td><del></del></td> <td><u> </u></td>	<del></del>	<u> </u>
VII-29         570           VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-71         599           VII-72         600 </td <td>VII-27</td> <td>568</td>	VII-27	568
VII-32         571           VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-48         584           VII-49         585           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-71         599           VII-72         600           VII-73         601 </td <td>VII-28</td> <td>569</td>	VII-28	569
VII-33         572           VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         583           VII-48         584           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604 </td <td>VII-29</td> <td>570</td>	VII-29	570
VII-34         573           VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         584           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604 </td <td>VII-32</td> <td>571</td>	VII-32	571
VII-35         574           VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-49         585           VII-50         586           VII-51         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-80         605 </td <td>VII-33</td> <td>572</td>	VII-33	572
VII-36         575           VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-47         585           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-77         604           VII-80         605           VII-81         606 </td <td>VII-34</td> <td>573</td>	VII-34	573
VII-39         576           VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-80         605           VII-81         606 </td <td>VII-35</td> <td>574</td>	VII-35	574
VII-40         577           VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-51         589           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608 </td <td>VII-36</td> <td>575</td>	VII-36	575
VII-41         578           VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-39	576
VII-42         579           VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-40	577
VII-43         580           VII-44         581           VII-45         582           VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-51         588           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-41	578
VII-44         581           VII-45         582           VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-42	579
VII-45         582           VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-43	580
VII-46         583           VII-48         584           VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-44	581
VII-48         584           VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-45	582
VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-46	583
VII-49         585           VII-50         586           VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-48	584
VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-49	
VII-52         587           VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-50	586
VII-53         588           VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-52	587
VII-54         589           VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         604           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	<del> </del>	588
VII-55         590           VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	VII-54	
VII-57         591           VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-75         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609	<b> </b>	<del></del>
VII-58         592           VII-59         593           VII-62         594           VII-63         595           VII-64         596           VII-65         597           VII-66         598           VII-71         599           VII-72         600           VII-73         601           VII-74         602           VII-76         603           VII-77         604           VII-80         605           VII-81         606           VII-82         607           VII-83         608           VII-84         609		
VII-59       593         VII-62       594         VII-63       595         VII-64       596         VII-65       597         VII-66       598         VII-71       599         VII-72       600         VII-73       601         VII-74       602         VII-75       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		<del></del>
VII-62       594         VII-63       595         VII-64       596         VII-65       597         VII-66       598         VII-71       599         VII-72       600         VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		
VII-63       595         VII-64       596         VII-65       597         VII-66       598         VII-71       599         VII-72       600         VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609	<del></del>	
VII-64       596         VII-65       597         VII-66       598         VII-71       599         VII-72       600         VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		
VII-65       597         VII-66       598         VII-71       599         VII-72       600         VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		
VII-66       598         VII-71       599         VII-72       600         VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		
VII-71       599         VII-72       600         VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		
VII-72       600         VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		
VII-73       601         VII-74       602         VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		
VII-74     602       VII-76     603       VII-77     604       VII-80     605       VII-81     606       VII-82     607       VII-83     608       VII-84     609		
VII-76       603         VII-77       604         VII-80       605         VII-81       606         VII-82       607         VII-83       608         VII-84       609		<del></del>
VII-77     604       VII-80     605       VII-81     606       VII-82     607       VII-83     608       VII-84     609		
VII-80 605 VII-81 606 VII-82 607 VII-83 608 VII-84 609		<del></del>
VII-81 606 VII-82 607 VII-83 608 VII-84 609		
VII-82 607 VII-83 608 VII-84 609		
VII-83 608 VII-84 609		
VII-84 609		·
VII-87   610		
	VII-87	610

VII-89	611
	611
VII-90	612
VII-91	613
VII-92	614
VII-93	615
VII-94	616
VII-96	617
VIII-09	618
VIII-10	619
VIII-11	620
VIII-12	621
VIII-13	622
VIII-15	623
VIII-16	624
VIII-17	625
VIII-18	626
VIII-19	627
VIII-20	628
VIII-21	629
VIII-23	630
VIII-24	631
VIII-25	632
VIII-28	634
VIII-29	635
VIII-30	636
VIII-31	637
VIII-32	638
VIII-33	639
VIII-34	640
VIII-36	641
VIII-37	642
VIII-38	643
VIII-40	644
VIII-41	645
VIII-42	646
VIII-43	647
VIII-45	648
VIII-46	649
VIII-47	650
VIII-48	651
VIII-50	652
VIII-51	653
VIII-53	654
VIII-54	655
VIII-55	656
VIII-56	657
VIII-56	
VIII-57	658
	659
VIII-59	660
VIII-60	661
VIII-61	662

<u></u>	
VIII-64	663
VIII-65	664
VIII-66	665
VIII-67	666
VIII-68	667
VIII-69	668
VIII-70	669
VIII-71	670
VIII-72	671
VIII-73	672
VIII-74	673
VIII-75	674
VIII-76	675
VIII-77	676
VIII-78	677
VIII-79	678
VIII-80	679
IV-02	681
IV-04	682
IV-13	683
IV-14	684
IV-17	685
IV-28	686
IV-31	687
IV-32	688
IV-38	689
IV-40	690
IV-42	691
IV-44	692
IV-47	693
IV-55	694
IV-56	695
IV-61	696
IV-64	697
IV-65	698
IV-72	699
IV-72	700
IV-80	700
IV-85	702
IV-93	703
IV-95	704
IV-96	705
V-03	706
V-04	707
V-07	708
V-08	709
V-09	710
V-12	711
V-18	712
V-20	713
V-24	714
	·

1 1/27	716
V-37	717
V-40	<u></u>
V-41	718
V-48	719
V-57	720
V-61	721
V-64	722 .
V-65	723
V-74	724
V-80	726
V-81	727
V-87	728
VI-13	870
VI-14	871
VI-16	873
VI-23	878
VI-24	879
VI-28	883
VI-32	885
VI-38	886
VI-39	887
VI-45	889
VI-46	890
VI-49	892
VI-50	893
VI-52	894
VI-53	895
VI-54	896
VI-55	897
VI-57	898
VI-58	899
VI-63	900
VI-65	902
VI-66	903
VI-67	904
VI-74	905
VI-75	906
VI-76	907
VI-80	908
VI-81	909
VI-85	910
VI-87	911
VI-88	912
VI-91	913
VI-94	914
VI-95	915
VI-96	916
I-13	1177
1-14	1178
I-30	1180

I-88	I-54	1181
III-20	I-88	
IV-15		
IV-26		
IV-62		
V-11         1188           V-28         1189           V-38         1190           V-45         1191           VI-47         1200           I-42         1332           I-52         1333           I-86         1336           I-95         1337           III-10         1342           III-60         1347           III-82         1348           III-92         1351           IV-23         1353           IV-34         1354           IV-35         1355           IV-41         1356           IV-45         1357           IV-82         1359           V-01         1361           V-02         1362           V-03         1363           V-17         1364           V-25         1365           V-35         1366           V-42         1367           V-47         1368           V-49         1369           V-58         1370           V-75         1372           V-91         1375           V-94         1376		
V-28         1189           V-38         1190           V-45         1191           VI-44         1193           VII-47         1200           I-42         1332           I-52         1333           I-86         1336           I-95         1337           III-10         1342           III-60         1347           III-82         1348           III-92         1351           IV-23         1353           IV-34         1354           IV-35         1355           IV-41         1356           IV-35         1357           IV-82         1359           V-01         1361           V-02         1362           V-03         1363           V-17         1364           V-25         1365           V-35         1366           V-42         1367           V-47         1368           V-49         1369           V-58         1370           V-75         1372           V-91         1375           V-94         1376		
V-38         1190           V-45         1191           VI-44         1193           VII-47         1200           I-42         1332           I-52         1333           I-86         1336           I-95         1337           III-10         1342           III-60         1347           III-82         1348           III-92         1351           IV-23         1353           IV-34         1354           IV-35         1355           IV-41         1356           IV-45         1357           IV-82         1359           V-01         1361           V-02         1362           V-03         1363           V-17         1364           V-25         1365           V-35         1366           V-47         1368           V-49         1369           V-58         1370           V-75         1372           V-91         1375           V-94         1376           VI-10         1379           VI-41         1381		
V-45         1191           VI-44         1193           VII-47         1200           I-42         1332           I-52         1333           I-86         1336           I-95         1337           III-10         1342           III-60         1347           III-82         1348           III-92         1351           IV-23         1353           IV-34         1354           IV-35         1355           IV-41         1356           IV-45         1357           IV-82         1359           V-01         1361           V-02         1362           V-03         1363           V-17         1364           V-25         1365           V-35         1366           V-42         1367           V-47         1368           V-49         1369           V-58         1370           V-75         1372           V-79         1373           V-90         1374           V-91         1376           VI-71         1388		
VI-44         1193           VII-47         1200           I-42         1332           I-52         1333           I-86         1336           I-95         1337           III-10         1342           III-60         1347           III-82         1348           III-92         1351           IV-23         1353           IV-34         1354           IV-35         1355           IV-41         1356           IV-35         1357           IV-82         1359           V-01         1361           V-02         1362           V-03         1363           V-17         1364           V-25         1365           V-35         1366           V-42         1367           V-47         1368           V-49         1369           V-58         1370           V-75         1372           V-91         1375           V-94         1376           VI-10         1379           VI-41         1381           VI-92         1388		
VII-47		
I-42		
1-52		
I-86		
III-10		
III-10		
III-60	<u></u>	
III-82		
III-92	<del></del> -	
IV-23       1353         IV-34       1354         IV-35       1355         IV-41       1356         IV-45       1357         IV-82       1359         V-01       1361         V-02       1362         V-06       1363         V-17       1364         V-25       1365         V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397		
IV-34       1354         IV-35       1355         IV-41       1356         IV-45       1357         IV-82       1359         V-01       1361         V-02       1362         V-06       1363         V-17       1364         V-25       1365         V-35       1366         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397		
IV-35         1355           IV-41         1356           IV-45         1357           IV-82         1359           V-01         1361           V-02         1362           V-06         1363           V-17         1364           V-25         1365           V-35         1366           V-42         1367           V-47         1368           V-49         1369           V-58         1370           V-75         1372           V-79         1373           V-90         1374           V-91         1375           V-94         1376           VI-10         1379           VI-41         1381           VI-72         1388           VI-79         1389           VI-90         1390           VI-93         1391           VII-25         1397		
IV-41       1356         IV-45       1357         IV-82       1359         V-01       1361         V-02       1362         V-06       1363         V-17       1364         V-25       1365         V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397	<u> </u>	
IV-45         1357           IV-82         1359           V-01         1361           V-02         1362           V-06         1363           V-17         1364           V-25         1365           V-35         1366           V-42         1367           V-47         1368           V-49         1369           V-58         1370           V-75         1372           V-79         1373           V-90         1374           V-91         1375           V-94         1376           VI-10         1379           VI-41         1381           VI-43         1382           VI-71         1387           VI-72         1388           VI-79         1389           VI-90         1390           VI-93         1391           VII-25         1397		
IV-82       1359         V-01       1361         V-02       1362         V-06       1363         V-17       1364         V-25       1365         V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-43       1382         VI-71       1387         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397	IV-41	
V-01       1361         V-02       1362         V-06       1363         V-17       1364         V-25       1365         V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-43       1382         VI-71       1387         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397	IV-45	1357
V-02       1362         V-06       1363         V-17       1364         V-25       1365         V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-43       1382         VI-71       1387         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397		1359
V-06       1363         V-17       1364         V-25       1365         V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-43       1382         VI-71       1387         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397	V-01	
V-17       1364         V-25       1365         V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-43       1382         VI-71       1387         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397		1362
V-25     1365       V-35     1366       V-42     1367       V-47     1368       V-49     1369       V-58     1370       V-75     1372       V-79     1373       V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397	V-06	1363
V-35       1366         V-42       1367         V-47       1368         V-49       1369         V-58       1370         V-75       1372         V-79       1373         V-90       1374         V-91       1375         V-94       1376         VI-10       1379         VI-41       1381         VI-43       1382         VI-71       1387         VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397	V-17	1364
V-42 1367 V-47 1368 V-49 1369 V-58 1370 V-75 1372 V-79 1373 V-90 1374 V-91 1375 V-94 1376 VI-10 1379 VI-41 1381 VI-43 1382 VI-71 1387 VI-72 1388 VI-79 1389 VI-90 1390 VI-93 1391 VII-25 1397	V-25	1365
V-47     1368       V-49     1369       V-58     1370       V-75     1372       V-79     1373       V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1397	V-35	1366
V-49     1369       V-58     1370       V-75     1372       V-79     1373       V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397	V-42	1367
V-58     1370       V-75     1372       V-79     1373       V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397	V-47	1368
V-75     1372       V-79     1373       V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1397	V-49	1369
V-79     1373       V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397	V-58	1370
V-79     1373       V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397	V-75	1372
V-90     1374       V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397		<del></del>
V-91     1375       V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397		<del></del>
V-94     1376       VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397		
VI-10     1379       VI-41     1381       VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397	<b></b>	<del></del>
VI-41 1381 VI-43 1382 VI-71 1387 VI-72 1388 VI-79 1389 VI-90 1390 VI-93 1391 VII-25 1397		
VI-43     1382       VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397		<del></del>
VI-71     1387       VI-72     1388       VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397		
VI-72       1388         VI-79       1389         VI-90       1390         VI-93       1391         VII-25       1397	<b></b>	
VI-79     1389       VI-90     1390       VI-93     1391       VII-25     1397		<del></del>
VI-90     1390       VI-93     1391       VII-25     1397		<del> </del>
VI-93 1391 VII-25 1397		
VII-25 1397		<u> </u>
		<u> </u>
VII-60 1398		
	VII-60	1398

VII-67	1399
VIII-22	1403
VIII-26	1404
VIII-39	1405
VIII-44	1406
I-37	1440
V-32	1445
V-52	1447
V-68	1448
V-92	1449
VI-42	1450
VI-78	1452
VII-86	1453 .
VII-88	1454
IV-29	1490
V-15	1491
V-39	1492
V-54	1493
V-59	1494
V-71	1495

Table 5

Samples

Diagnosis	No. of women
Normal /Benign	42*
DCIS	3
Invasive cancer	26

<sup>\*</sup> From one woman, whole blood was collected at weeks 1,2,3,4,5 following menstruation. Hence, the number of unique normal/benign samples tested in the experiment is 75

Information about women with breast cancer

		711021 111111	orcast cancer		γ ····································
Sample	AGE	Stage	Cancer type	Size hist. (mm)	Nodes
1	51	11	IDC	20	1/7
2	84	11	IDC	22	2/2
3	50		DCIS+ 1 IDC	>50 DCIS; 5 x 14	0/7
4	47	1	IDC	15	0
5	69	Ш	ILC g.2 + tubular adenocarcinoma	50 + 3	1 av 12 + 1 av 7
6	50	11	IDC	24	0
7	65	ł	IDC	15	0
8	63	1)	IDC	23	0
9	55	1	IDC + DCIS	4	0 av 1
_	52	0	DCIS + small colloid carcinoma foci	50 + 3	0
10	60	<b>i</b> 1	IDC	24	0
	54	1	IDC	11	0
12	54	0	DCIS	20	0
13	49	0	DCIS	9	0
14	48	1	IDC	4	0
	56	1	IDC	4	0
16 17	68	<del></del>	IDC	14	0
18	68	<u> </u>	IDC	7	0
19	63	1.	IDC	10	0
	45		IDC	19	1
20	57	111	IDC	60	8/20
22	55	11	IDC/DCIS	35 +55	0
	- 33		IDC/extensive		<del> </del>
23	71	1	DCIS	8	0
24	56	1	· IDC	9 .	· ?

25	66	11	IDC	26	0
26	66	1	IDC	15	7
27	61	I	IDC	9	<u>-</u>
28	?	?	?	7	
29	65	1	IDC	11	· · ·

## Other diseases /conditions present in the women tested

Other diseases /conditions present in the women tested

	Cuter discases /conglions
Disease/condition	
Diabetes	
Asthma	
Ulcerous colitis	
Hemochromatose	
Crohn's disease	
Fibromyalgia	
Psoraiasis	
Atopic eczema	
Rheumatism	
Allergies	

Prior history of cancer in the women tested

	oor in the wonten tested
Cancer type	No. of women
Breast	3
Colon	2
Stomach	1 .
Skin	1

## Table 6

Number of samples tested by double cross validation and success of the diagnostic test for breast cancer based on selected informative genes

Number of samples tested by double cross validation

e samples 75	ested 46		82
Number of unique samples tested	Number of unique non cancer samples tested	Number of cancer samples	naisan

Success of the diagnostic test for breast cancer based on selected informative genes

Occurrence in	Number of Informative				False Positive	False	
percentage*	probes	Specificity	Sensitivity	Accuracy	rate	rate	Total error rate
100.00	23	84.78	75.88	81.33	15.22	24.14	18.67
90:00	\$	91.30	79.31	86.67	8.70	20.69	(3.33
00'00	51	86.96	79.31	84.00	13.04	20.69	16.00
70.00	72	89.13	75.86	84.00	10.87	24.14	16.00
60.00	58	89.13	75.86	84.00	10.87	24.14	16.00
50.00	59	89.13	75.86	84.00	10.87	24,14	16.00
40.00	63	89.13	75.86	84.00	10.87	24.14	16.00
30.00	98	88.38	75.86	82.67	13.04	24.14	17.33
20.00	74	89.13	75.86	84.00	10.97	24.14	16.00
10.00	79	89.13	75.86	84.00	10.87	24.14	16.00
5.00	8	88.38 38.38	79,31	84.00	13.04	20.69	16.00
1.33	139	84.78	72.41	. 00:08	15.22	27.59	20.00

\*100% = Genes appearing in all the 75 cross validated models; 90% = Genes appearing in at least 68 out of 75 cross validated models; 5% = Genes appearing in at least 4 out of 75 cross validated models; and so on,

Table 7

Double cross-validation and details of the success of the diagnostic test for Alzheimer disease based on the expression 182 informative genes

Validation Result

Total number of samples tested	14
Number of Alzheimer's disease	
samples tested	7
Number of Alzheimer, s disease	
samples incorrectly predicted	-
Number of non Alzheimer's	
disease samples tested	7
Number of non-Alzheimer's	
disease samples incorrectly	
predicted	0

# Success of diagnostic test

renormance	Description	%
	Percentage of the total	
	number of predictions that	
Accuracy	were correct	92.9
	Percentage of positive	
	cases that were correctly	
Sensitivity	Identified	85.7
	Percentage of negatives	
	cases that were correctly	
Specificity	predicted	5
	Percentage of negatives	
	cases that were incorrectly	
False positive rate	classified as positive	0.0
	Percentage of positives	
	cases that were incorrectly	
False negative rate	False negative rate classified as negative	14.3
	Percentage of the total	
Total error rate	cases incorrectly predicted	7.1

Table 8

Some relevant features of the blood donors. B, Female donors with breast cancer; N, Female donors with suspected mammogram but no breast cancer; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; na, not available nd, not determined; ++, no degradation of mRNA and no ribosomal contamination in the sample, +, no degradation of mRNA but ribosomal contamination in the sample.

·		AGE	Cancer type /breast abnormality	Size Hist, (mm)	mRNA Quality
1	B1	na	IDC	5	++
2	B2	49	DCIS	8	nd
. 3	B3	54	IDC	18	++
4	B4	59	IDC	12	+
5	B5	61	DCIS+micro invasive cancer	15+1.5	++
6	B6	55	IDC	12+17	nd
7	B6		IDC	12+17	nd
8	N1	45	Fibroadenoma	-	nd
9	N2 ·	52	na	-	+
10	N3	55	Cyst	-	++
11	N4	54	na		++
12	N5	51	Benign ductal epitelhelium	-	nd
13	N6	57	Benign	-	nd
14	N7	50	na	- 1	++
15	N8	52	na	-	+

Table 9

List of sequence of probes informative for both alzheimer and breast cancer disease

Clone ID	Sequence ID
1-24	308
1-25	309
I-28	310
1-48	321
1-60	327
1-72	333
I-81	338
1-82	339
11-02	360
11-03	361
11-06	364
11-07	365
11-10	368
II-21	378
11-23	. 380
11-24	381
11-25	382
11-27	384
11-33	390
11-34	391
11-41	397
11-42	398
11-46	401
11-47	402
11-48	403
11-52	406
11-57	411
11-58	412
11-59	413
11-60	414
II-61	415
11-62	416
11-64	418
11-67	421
11-69	423
11-70	424
11-74	428
11-80	434
11-82	436
11-84	438

11-87	441
11-88	442
11-96	450
III-01	452
111-02	453
111-06	458
111-08	460
III-12	463
III-13	464
III-17	468
III-18	469
III-21	471
III-23	473
111-24	474
III-25	475
111-26	476
111-27	477
111-28	478
III-28	479
	482
111-32	<del></del>
111-33	483
111-35	485
111-39	487
111-40	488
111-42	489
111-45	492
111-46	493
111-47	494
111-48	495
111-56	503
111-57	504
111-58	505
111-59	506
111-61	507
111-62	508
111-63	509
111-64	510
111-66	512
111-67	513
111-70	515
111-74	518
111-75	519
111-78	521
111-80	523
III-81	524
111-85	526
111-86	527
111-88	529
111-89	530
	532
111-93	534
111-95	1 334

111-96	535
IV-04	682
IV-13	683
IV-14	684
IV-17	685
IV-31	687
IV-32	688
IV-38	689
IV-42	691
IV-47	693
IV-61	696
IV-64	697
	699
IV-72	<del> </del>
IV-80	701
IV-85	702
IV-93	703
IV-96	705
V-03	706
V-04	707
V-07	708
V-08	709
V-12	711
V-24	714
V-41	718
V-57	720
V-61	721
V-64	722
V-65	723
V-74	724
V-80	726
VI-03	341
VI-04	342
VI-07	344
VI-08	345
VI-09	346
VI-12	869
VI-14	871
VI-19	349
VI-20	350
VI-21	351
VI-23	878
VI-25	353
VI-26	354
VI-48	359
VI-50	893
VI-53	895
VI-74	905
VI-76	907
VI-87	911
VI-88	912
VI-95	915
	<del></del>

VII-02	547
VII-03	548
VII-06	551
VII-08	553
VII-09	554
VII-10	555
VII-11	556
VII-15	559
VII-17	560
VII-19	562
VII-21	564
VII-22	565
VII-23	566
VII-24	567
VII-27	568
VII-29	570
VII-32	571
VII-33	572
VII-36	575
VII-39	576
VII-41	578
VII-42	579
VII-42	580
VII-43 VII-46	583
<del></del>	<del> </del>
VII-48	584
VII-49	585
VII-54	589
VII-57	591
VII-58	592
VII-59	593
VII-62	594
VII-63	595
VII-64	596
VII-66	598
VII-72	600
VII-73	601
VII-77	604
VII-80	605
VII-82	607
VII-87	610
VII-90	612
VII-91	613
VII-92	614
VII-93	615
VII-96	617
VIII-09	618
VIII-10	619
VIII-13	622
VIII-16	624
VIII-20	628
VIII-21	629

VIII-23	630
VIII-24	631
VIII-25	632
VIII-28	634
VIII-29	635
VIII-30	636
VIII-31	637
VIII-32	638
VIII-33	639
VIII-34	640
VIII-38	643
VIII-40	644
VIII-41	645
VIII-46	649
VIII-48	651
VIII-55	656
VIII-57	658 .
VIII-59	660
VIII-60	661
VIII-61	662
VIII-64	663
VIII-66	665
VIII-73	672
VIII-74	673
VIII-76	675
VIII-80	679

- 124 -

Nucleotide sequences

Sequence ID - 93 nt: 405

GGATCCTGTGGCCCACAGAGCTGCCCCAGCAGACGCTCCGCCCCACCCGGTGATGG

AGCCCCGGGGGGACAATCGTGCCTGGGGAGGAGCAGGGTACAGCCCATTCCCCCAG

CCCTGGCTGACCTGGCCTAGCAGTTTGGCCCTGCTGGCCTTAGCAGGGAGACAGGG

GAGCAAAGAACGCCAAGCCGGAGGCCCGAGGCCAGCCGGCCTCTCGAGAGCCAGAG

CAGCAGTTGAATGTAATGCTGGGGACAGGCATGCTGCCGCCAGTAGGGCGGGACC

CGGACAGCCAGGTGACTACCAGTCCTGGGGACACTCACCATAAACACATCCCCA

GGCAGGACAGATCGGGGAAGGGGTGTGTACCAGGCTATGATTTCTCTTGCATTAAA

ATGTATTATTATT

Sequence ID - 108 nt: 550

GGCTTTGACAGAGTGCAAGACGATGACTTGCAAAATGTCGCATCTGGAACGCAACA

TAGANACCATCATCAACACCTTCCACCAATACTCTGTGAAGCTGGGGCACCCAGAC

ACCCTGAACCAGGGGGAATTCAAAGAGCTGGTGCGAAAAAGATCTGCAAAATTTTCT

CAAGAAGGAGAATAAGAATGAAAAGGTCATAGAACACATCATGGAGGACCTGGACA

CAAATGCAGACAAGCAGCTGAGCTTCGAGGAGTTCATCATGCTGATGGCGAGGCTA

ACCTGGGCCTCCCACGAGAAGATGCACGAGGGTGACGAGGGCCCTGGCCACCACCA

20 TAAGCCAGGCCTCGGGGAGGGCACCCCCTAAGACCACAGTGGCCAAGATCACAGTG

GCCACGGCCACGGCCACAGTCATGGTGGCCACGACCACTAATCAGGAGGC

CAGGCCACCCTGCCTNTACCCAACCAGGGCCCCGGGGCCTGTTATGTCAAACTGTC

TTGGCTGTGGGGCTAGGGGCTGGGGCCAAATAAAGTCTCTTTCTCC

- Sequence ID 192 nt: 286

  CCGGTAATAGAATAGAAAAGGGAGAGTGTCTTCATGCAATGTGGCATCCTGGATTG

  GGTCTCGNNACAAAAACAGGACATTAGTGGGAAAATTGGAAATCTGAAAAAAGTCT

GAATTTTAGTTAATATACCAATTTCAGTCTCTTGGTTTTGACAGATGTACCATGGT GATGTAAGATGTTGACCTTGGGGTAGGCTGGGTGAAGGGTATACAGGAACTCTTTG TACTATCTCTGCAACTTCTCTGTAAATCTAGTATCATTCCAAAATAAAAGTTTATT TAATTT

5

10

15

Sequence ID 250

GTGGAAGTGACATCGTCTTTAAACCCTGCGTGGCAATCCCTGACGCACCGCCGTGA
TGCCCAGGGAAGACAGGGCGACCTGGAAGTCCAACTACTTCCTTAAGATCATCCAA
CTATTGGATGATTATCCGAAATGTTTCATTGTGGGAGCAGACAATGTGGGCTCCAA
GCAGATGCAGCAGATCCGCATGTCCCTTCGCGGGAAAGCTGTGGTGCTGATGGGCA
AGAACACCATGATGCGCAAGGCCATCCGAGGGCACCTGGAAAACAACCCAGCTCTG
GAGAAACTGCTGCCTCATATCCGGGGGAATGTGGGCTTTTGTGTTCACCAAGGAGGA
CCTCACTGAGATCAGGGACATGTTGCTGGCCAATAAGGTGCCAGCTGCTGCCCGTG
CTGGTGCCATTGCCCCATGTGAAGTCACTGTGCCAGCCCAGAACACTGGTCTCGGG
CCCGAGAAGACCTCCTTTTTCCAGGCTTTAGGTATCACCACTAAAATCTCCAGGGG
CACCATTGAAATCCTGAGTGATGTGCACTGATCAAGACTGG

Sequence ID 299

30

- 126 -

Sequence ID 302

AGTAGAGACGGGGTTTCACTGTGTTAGCCAGGATGGTCTCGATCTCCTGACCTCGT GATCCGGCCACCTCGGCCTCCCGAAAGTGCTGGGATTACAGGCGTGAGCCACGGCG CCCAGCCCCAGCCTGTCACTTAAACTGATAAACGACAGATTAACAGTAGAAAAATT TTATTTTGCATACATAATGAGGCTTCACAAAAGAGAAGTGAAAACCCAAGTAGGAG TTTAGGGCTGGGGGCTTATATACCATTTAACAAGGGGTGATAAATTGTAAGAGAAT AG

### Sequence ID 304

- Sequence ID 306

  CTTTTCCTCCCGCTGTCCCCCACGGAGGGGACTGCTCTCCCCCGCTGCATCCTTTC

  TGTGAGGTACCTTACCCACCTCAGCACCTGAGAGGGTGAAATAGAATTCTAACCTC

  GACATTCGGGAAGTGTTTTTGAGAAGTCTCGGTCGGTAAGGGAAGTCTTCCAAGTC

  CGTGCAGCACTAACGTATTGGCACCTGCCTCCTCTTCGGCCACCCCCCAGATGAGG

  CAGCTGTGACTGTCCAAGGGAAGCCACGACTCTGACCATAGTCTTCTCTCAGCTT

  CCACTGCCGTCTCCACAGGAAACCCAGAAGTTCTGTGAACAAGTCCATGCTGCCAT

  30

  CAAGGCATTTATTGCAGTGTACTATTTGCTTCCAAAGGATCAGGCCCTGAGAACAA

  TGACCTTATTTCCTACAACAGTGTCTGGGTTGCGTGCCAGCAGATGCCTCAGATAC

  CAAGAGATAACAAAGCTGCAGCTCTTTTGATGCTGACCAAGAATGTGGATTTTGTG

AAGGATGCNCATGAANAAATGGACNAGCTGTG

- 127 -

TTTATTTGCTATATCATCTAATTTAGTTTGAATATTCCATAATTTACTTAATTAGT CCTGTATGGAGACCTAGCTCTTCTCAGTGTCTACTATTATAAACAATGCTACAGTG AATATTGGTGNATAAATCCATACNCACCACGTACATATCTTAAGTTCTGGAAGAGA TATTGCTAAACCAGAAGATAACCTGCATTTAAAATTTGACTGCTAGGGNCAGGGNC ACATTTAATTAAATTAGAACAANGAATGCATAATGNC

Sequence ID 309

CCGGAATCGCGGCCGCGTCGACGAAAATATGTGCCCTGGCCAACTCCACAGGACTA GTTCTAGGCAATCTGAAGGAAAACCAGAAAATGTGAATTTCTCTTCCCTCAAAAAGC . 10 TATACTGAAGTAGTATTTAATATTCAAGTACTTGTAAATTTGCAGAACAGTACTTT TTAATTTGACCCATGAATTCTATTTAAATTTGTCACTTAATATTTAGCCAAGAAGC ATATTTTTAACTTTTTTCTAATTTGAAAAGTAATACAGGCATATGGTATTTTAAA AATGAAACAACACAAAGGGATATGTTTTGAAAAGTGGTCTTGCCATCCCTGAACTG TAATCATCCCTAACATATTCATACCTGTTTTCATTTTAAAAGTTGGGTCAGTTTTT 15 TTATTAGTACATGTATTTCTATCCTACTGATTTATTTGCTATATCATCTAATTTAG TTTGAATATTCCATAATTTACTTAATTAGTCCTGTATGGAGACCTAGCTCTTCTCA GTGTCTACTATTATAAACAATGCTACAGTGAATATTGGTGNATAAATCCTACACAC CACGTAACATATCTTAAGTTCCTGGAAGAGATATTGCTAAACCAGAAGATAACCTG 20 CATTTAAAATTTGACTGCTAGGGTCAGGGTCACATTTAAATTAAATTAGAACAAGG AATGCATAATGTCTTCGATAGCAATCTATTCAAGGTGCACCGTGGTCACAAAGGAA AGCAAAACTGTC

Sequence ID - 310 nt:564

Sequence ID 311

10

15

35

### Sequence ID 314

20 CTTTTCCTCCCGCTGTCCCCCACGGAGGGGACTGCTCTCCCCCGCTGCATCCTTTC
TGTGAGGTACCTTACCCACCTCAGCACCTGAGAGGGTGAAATAGAATTCTAACCTC
GACATTCGGGAAGTGTTTTTGAGAAGTCTCGGTCGGTAAGGGAAGTCTTCCAAGTC
CGTGCAGCACTAACGTATTGGCACCTGCCTCCTCTTCGGCCACCCCCCAGATGAGG
CAGCTGTGACTGTGTCAAGGGAAGCCACGACTCTGACCATAGTCTTCTCTCAGCTT

25 CCACTGCCGTCTCCACAGGAAACCCAGAAGTTCTGTGAACAAGTCCATGCTGCCAT
CAAGGCATTTATTGCAGTGTACTATTTGCTTCCAAAGGATCAGGCCCTGAGAACAA
TGACCTTATTTCCTACAACAGTGTCTGGGTTGCGTGCCAGCAGATGCCTCAGATAC
CAAGAGATAACAAAGCTGCAGCTCTTTTGATGCTGACCAAGAATGTGGATTTTGTG
AAGGATGCACATGAAGAAATGGAGCCAGGCTGTGGAAGAATGTGACCCTTACTCTGG
30 CCTCTTGAATGATACTGAGGAGAACAACTCTGACCACAATCATGAGG

### Sequence ID 315

TGGTACAGATACAAACTGGACTCTCAGGACAAAACGACACCAGCCAAACCAGCAGC
CCCTCAGCATCCAGCAGCATGAGCGGAGGCATTTTCCTTTCTTCGTGGCCAATGC
CATAATCCACCTCTTCTGCTTCAGTTGAGGTGACACGTCTCAGCCTTAGCCCTGTG
CCCCCTGAAACAGCTGCCACCATCACTCGCAAGAGAATCCCCTCCATCTTTGGGAG
GGGTTGATGCCAGACATCACCAGGTTGTAGAAGTTGACAGGCAGTGCCATGGGGGC

- 129 -

AACAGCCAAAATAGGGGGGTAATGATGTACGGGCCAAGCACTGCCCAGCTGGGGGT CAATAAAGTTACCCTTGTACTTG

Sequence ID 316

Sequence ID 321

Sequence ID 322

CTTTATTGAGGTTCGAAATTAATAAAGAAATAAAAGAAATGTATCTTCATT 25 CTGTATGTTAGTGTTTTAATTACCCTTAGAATATATGGATAAAAAATACTATTCTT TGTCTTGGAGAAGGTAAGAGTCTAGTTAGATGAATAAGGGTTATCTATGTAGAACA ACTAGAGAATGAGAAGAGCTTATGAGATTGAGTACTACGTTATGCAGTAGAGTA GCACGTCATCTGCTACTGAGTATGGTGTGATAACATTGTGTAACAGGAAAGTATGA 30 TCAATATCTACTTAAAATTAAGGACAATATTAGCACTACATTGCTTTATTTTAAAG TAAAAATTAGAGAACTAAACACAAGCATTGTAAGTACAATAAAAGCTGATCTTTCT AGTTAAGCAGAATAATACATGTTCAAGCATCTGCTAAATCATTAAATATAAGAATA TAGGGGTTTTCTATAATCTTATTTTCTTTGGAAGAGTACCTCATTTTCAAGANGAG AAGTTTCTAATTGCCACTTCTTTAAAAATAAAACAGGGTTTTAATGTTCCCAGCAC 35 AAAAATTAATATCTCTTCAAAAAGTCTCTTGTGATTAAGTTTGAATCCCTTGTCAT ACTGCTTCTAATATTGACACTGACCTCCTTAGGTATTTTTCAGGGGGTTATAATCTT TTCTTAAGGTATCTTTTTTCAAGAATTGGATACCTTGGGCTT

Sequence ID 323

CGCGTCGACTTTTAAAGTCATCTCTATAGGAAGGTGCTGGGCAGGGATCCCAGAGA
AAGAAAGGGTCCAAGACTCCATTAACTGCCCTGGATGAAGGGCACTGCTACAGCAG
CTAGTACCAGAGACTCTCCTATCTCACGGTTGAGGCAGACCCAGGATAGAATAGAG

5 AATAAAAGGAATGCTTATAGGAAACAATTTTGTATGGAATGCTAGATGGCCAAGCC
TCAGCCTTTGGTCCAGTGCAACCCTTGCCTCGCTTGTCAACAGTGAAAAAATTAGTT
TGGTTAGAAGAACCATCTGGAAACACACCAGCTTCTGCTACCTTCATGCTCATTGT
TAAAAAAAGATTAACCAGTGTGAACATTCTGATCTGTTAATTCCAGGGACTGTTTT
CTTTCCAATGGACTGTTTGTTGGTAGAATAACCCCCAAAAGCTCAAAGCTAAAATG
CATCATCAGTCCTAGTCGGCAGTTCCTTAAGAATGGACTGGCGGCGTGGTTGAGCT
GATATGGAAAAGCTGCACCTTCCTGCAGAAGATCAACTGACCTGCTATCCCACCCC
AAATTCAACCTGAGGTATATTTCAGTGAAGCAGGTAGCTGTCTTCTCAAAGCAGA
GAAGCAGTTTTAAGAACCAAAAAGGTAGAGGAAATCTA

- 15 Sequence ID 324 GTTTGTTACAGGCAGAATTGGATAGATACAGCCCTACAAATGTATATGCCCTCCCC TGAAAAAATTGGATGAAAATCTGCACAGCAAAGTGAAACACACAGATAATAGGAA CAAAATGTAGTTCCCATGTGCCAAACAAAATAAATGAAATCTCTGCATGTTTGCAG CATATCTGCCTTTTGGGAATGTAATCAAGGNATAATCTTTGGCTAGTGTTATGTGC  $\tt CTGTATTTTTTAAAATGGTACACCAGAAAAGGACTGGCAGTCTACTTACCATA$ 20 GTTAAACTTCACCCTCTTTAATTTCACAACATATTCTTTGGAAGCAGGAAGAAATG CTCATAAAGAGGATCAGACCTTCTTTCCCGTGAAACCAGTATTTGGCGCCATATAT AAGCCTGGTTAAATTGGTCATCTAAAGCTGTCAAATAAGACATTCTGTGAAAGGTA AACATCGAAACTGGTTATAAGTAAAACCATCAAGCCAACAACAGGGTCTTGAGATA  ${\tt ACCTTTGAAGCTTATTGTCTGGCCTGCACCAGAAGATGTCTGCATTACTCATTGCT}$ 25 AAAAATGTGTACACAGAACTGCACTAGGATTAATTGGTTCAAGAAGAAATTTAAAC  ${\tt TTACGTTTGGGTTTCCATACAGCACTCTATTGAATACATGCATCTGAATTTAAGTT}$ **GCAA**

- 131 -

5

10

15

20

25

30

Sequence ID 327

CGGCTACCGACAGAAGGACTATTTCATCGCCACCCAGGGGCCACTGGCACACACGG
TTGAGGACTTCTGGAGGATGATCTGGGAGGGGAAGTCCCACACTATCGTGATGCTG
ACGGAGGTGCAGGAGAGAGAGAGAGAGAGATAAATGCTACCAGTATTGGCCAACCGAGGG
CTCAGTTACTCATGGAGAAATAACGATTGAGATAAAGAATGATACCCTTTCAGAAG
CCATCAGTATACGAGACTTTCTGGTCACTCTCAATCAGCCCCAGGCCCGCCAGGAG
GAGCAGGTCCGAGTAGTGCGCCAGTTTCACTTCCACGGCTGGCCTGAGATCGGGAT
TCCCGCCGAGGGCAAAGGCATGATTGACCTCATCGCAGCCGTGCAGAAGCANCAGC
AGCAGACAGGCAACCACCCCATCACCGTGCACTGCAGTGCCGGAGCTTGGCGAACA
GGTACATTCATAGCCCTCAGCAACATTTTGGAGCGAGTAAAAGCCGAGGGACTTTT
ANATGTATTTCAAGCTGTGAAGAGTTTACGACTTCAGAGACCACATATGGTGCAAC
CCTGGAACAGTATGAAATGTGCTACAAAGTGGTACAAGATTTATTGATATATTTCT
GATTATGCTAATTTCAATGAAGATCCTGCCTTAAATATTTTTTAATTTAATTGCAN
AT

Sequence ID 328

CAAGACTCCATCTCAAAAAAAAAAAAAATCTACAGTGCTGAGTATATAAAATTAT

TAACACATTTCACAACAATATGTGTTTGTGGAGTTAAATATTTTTTTGTCTTTAAAA

CAGGTAATTTTAGTGCATACTTAATTTGATGATTAAATATGGTAGAATTAAGCATT

TTAAATGTTAATGTTTGTTACATTGTTCAAGAAATAAGTAGAAATATATTCCTTTG

TTTTTTATTTAAATTTTTGTTCCTCTGTAAACTAAAAGAACACGAAGTAATTGGTC
ACAATTACTGGTGTTTAACTGCCAAATATGGGTAAATAAGGGAAAATTTTGTTTAA
TATTTAGTCCTTCTGAGATGGCTTGAATATTTGAATTTTGTTGTACGTCTATACTG
GGTAGTCACAAGTCTTATAAAACACTTTAGAGGAAAGATGGATTTCAGTCTGTATTT
TTAAACATCATTTATTTTAAATCTGGTGCTGAAAAATAAGAAAAAAATTAAACTGC
ATTCTGCTGTTCTTCTTTANAAGCATTCCTGCGTAAATACTGCTGTAATACTGTCA
TGCAAAGTGTATCCTTTCTTGTCGTATCCTTTTTGGGGCAGTGGTTTTT

### Sequence ID 330

- - Sequence ID 331
  - GCCGCGTCGACCTGCATGAGCCACAGTTTCTTGACTGGAGGCCATCAACCCTCTTG 20  $\tt GTTGAGGCCTTGAGCCCTGACATGTGCTTGGGCACTGGTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGCCTTGGGGGCCTTGGGGGCCTTGGGGGCCTTGGGGGCCTTGGGGCCTTGGGGGCCTTGGGGCCTTGGGGGCCTTGGGGGCCTTGGGGGCCTTGGGGGCCTTGGGGGCCTTGGGGGCCTTGGG$  $\tt CTGAGGTGGCCTCCTGATCAGGGACCCTCCCCGCTTTCCTGGGCCTCTCAG$ TTGAACAAAGCAGCAAAACAAAGGCAGTTTTATATGAAAGATTANAAGCCTGGAAT AATCAGGCTTTTTAAATGATGTAATTCCCACTGTAATAGCATAGGGATTTTGGAAG CAGCTGCTGGTGGCTTGGGACATCANTGGGGCCCAAGGGTTCTCTGTCCCTGGTTCA 25 ACTGTGATTTGGCTTTCCCGTGTCTTTCCTGGTGATGCCTTGTTTGGGGTTCTGTG GGTTTGGGTGGGAAGAGGGCCATCTGCCTGAATGTAACCTGCTAGCTCTCCGAAGC CCTGCGGGCCTGGTGTGAGCGTGTGGACAGTGGTGGCCGCGCTGTGCCTGCT CGTGTTGCCTACATGTCCCTGGCTTGTTGAGGCGCTGCTTCAACCTGCACCCCTCC 30  $\tt CTATGCCTTTTGGCTTCCTGGTAGAAGGCGGGATGCCCAAGGGTCTGCCTGGGTGT$ GGATTGGATGCTTGGGGGTGTGGGGGCTTGGAAACTGTCTTGTGGCCCACTTGGGCCC C

### Sequence ID 335

35 CCCGCGTCGACTTTTAAAGTCATCTCTATAGGAAGGTGCTGGGCAGGGATCCCAGA GAAAGAAAGGGTCCAAGACTCCATTAACTGCCCTGGATGAAGGGCACTGCTACAGC AGCTAGTACCAGAGACTCTCCTATCTCACGGTTGAGGCAGACCCAGGATAGAATAG

- 133 -

AGAATAAAAGGAATGCTTATAGGAAACAATTTTGTATGGAATGCTAGATGGCCAAG
CCTCAGCCTTTGGTCCAGTGCAACCCTTGCCTCGCTTGTCAACAGTGAAAAATTAG
TTTGGTTAGAAGAACCCATCTGGAAACACCCCAGCTTCTGCTACCTTCATGCTCATT
GTTAAAAAAAAGATTAACCAGTGTGAACATTCTGATCTGTTAATTCCAGGGACTGTT
TTCTTTCCAATGGACTGTTTGTTGGTAGAATAACCCCCAAAAGCTCAAAGCTAAAA
TGCATCATCAGTCCTAGTCGGCAGTTCCTTAAGAATGGACTGGCGGCGTGGGTGAG
CTGATTTGGAAAAACTGCCCTTCTGCAAAAAAACACTGGCCTGCTTTCCA

### Sequence ID 337

5

25

30

35

### Sequence ID 338

10

Sequence ID 339

TTTTTTTTAAATAAAGCTGTCGGCACTCAAGGGTAATTTCATATCAGTGTGNTCT
ACAAGCTGGGGGAAAATGAGTTCTAATTGTCANAGCTACCAAATCCTTCACCTTTA
GCATAAAGGTTTAAAGATATCACAAAGATGCCAAGTGATTAATAATGTTTTAAACC
ACCCCTTTTTCTGTCTGAAAAAACAACTAAAACAATATTACAACAGTATAGTTACA
GAAGGGTTCTATTTTCATATGTTTTATGCACACTGTGCCTCAAAGGTACTATTTAA
ATATATATACTTTTGAGGGGGGTGGCTAATGCAGAAACACCCAAGACCTAAGGAAGA
TACAACCCCATTTCTAGGTGTGAGGTCTAAATGCTTCACACACCCACTTGTGACCT
TTTTTCATGAAGAATCATAACACTGTGCAGTGAGAAACAGTGGCAAAGCAATACTG
AAAGCATTTTAAATTATTTACTAGGTTAAAAGGGTGAACTGATACTTTAAATACAT
CAAATTTCATCAT

Sequence ID 360

- GCAAGTGAGAGCCGGACGGGCACTGGGCGACTCTGTGCCTCGCTGAGGAAAAATAA

  CTAAACATGGGCAAAGGAGATCCTAAGAAGCCGAGAGGCAAAATGTCATCATATGC

  ATTTTTTGTGCAAACTTGTCGGGAGGAGCATAAGAAGAAGCACCCAGATGCTTCAG

  TCAACTTCTCAGAGTTTTCTAAGAAGTGCTCAGAGAGGTGGAAGACCATGTCTGCT

  AAAGAGAAAGGAAAATTTGAAGATATGGCAAAAAGCGGACAAGGCCCGTTATGAAAG

  AGAAATGAAAACCTATATCCCTCCCAAAGGGGAGACAAAAAAAGAAGTTCAAGGATC

  CCAATGCACCCAAGAGGCCTCCTTCGGCCTTCTTCTTCTTCTGCTCTGAGTATCGC

  CCAAAAATCAAAGGAGAACATCCTGGCCTGTCCATTGGTGATGTTGCGAAGAAACT

  GGGAGAGATGTGGAATAACACTGCTGCAGATGACAAGCAGCCTTATGAAAAGAAGG

  CTGCGAAGCTGAAGGAAAAATACGAAAAGGTTA
- 25 Sequence ID - 361 nt: 622 CTGTNATNGAATCTGCTTGTNACTNAAATGCTAAACTCAATTCTGTAATTCAATAG GTGCACCTNTCTGAGAAACATANNAGACAATGAGGAAAAGGATTCANCATTCCGTG GAATTTGTACCATGATCAGTGTGAATCCCANTGGCGTAATCCAAGTAAGATGTTCA CAAAGATTTGTTTTAATGTCTAATTAATAAAATTTTAAAGGAAGAAACATTCTAA  ${\tt TACTTTAATTAAAAAAGTTAACTATTTTCAAAGGTATCAAAATACAGTTAAACCT}$ 30 TTTTTTTTGTCATGAAATGAGATAGTAACAGCAGATTGGGACAACAAGGTTATATT ACTTTGTCCCTGCCTCCCATCCCTGGATATCANGTTTGTGGATATCTACAGTTAAT 35 AGAGTGACCAAATAGTAGGAATACTGTCTCTCTATTCTGAATAAAATACTTTGAAT CAGATTTAGAAATAATGAATAAAATACAAATCACCATTGAAATTGCTCTAATTTTG AGAGCT

- 135 -

Sequence ID - 363 nt: 628 ATCACNTGAGGCAAGAGTTTGAGCCAGCCTAGCTAACATGGTGAAACCCCATCTCT ACAAAAATATAAAAATTAGCCTGGGTGGTGATGGGCACCTGTAACCCCAGCTACTC  ${\tt GGGAGGCTGAGGTAGGAGATCACTTGAACCCGGGAGATGGAGGTTGCAGTGAGCC}$ AAGATCGTGCCACTGCAGCCTGTGTGACAGAACAAGACTCTGTCTCAAAAA 5 AAAATAATAATAATAATAAAAAAGGAATAACATAGCTAGGAATAAATTTAA ATTATAGACCCAAATAAAATAAATAAAAGACATTCTGTGTTTTAGGGAAAGAAG ACTTAATATTGTTAAGATGTCAATACTACCCAAAGTGATCTACAGATTCAACATAA TCCCTATCAAAATTCCAACAGCCTACTTTGTAGAAATGGAAAAGCCAATTTTCAAA 10 TTCAGATGGAATTGCGAGGGTTCTGAATAACAAAACAATCTTGGGGAAAAAAA CAAAAAACAAAGTCAAAGAACTCACACTTCTCTATTTATAAATTTACTACAAAGTT ATAGTAATCAAA

15 Sequence ID - 364 nt: 528 TGAACATCCAGCCATGTCATTTCTTCCATTCCTGCCCTGGAGTAAAGTAGATTTAC TGAGCTGATGACTTGTGCATTTGTACATTGCAACCTTAGCTTACCTCTTGAAGC ATGTAGAGCATTCACCACCACCACCACTGTT TCGTGGTCTGTCTCCTGTGCCACCCCCACCCCATCAGGTGGGCCTTTTGCAA 20  $\tt CTCCATCCCAGTTCACCTTTTCAGAAATGGCCCCTCAGTCAACTCTTCCCTTTTCT$ CCTGGCTTTTTATTTCTCCCAGTCTCTTAAGAGTATCCTTAGCTTTAAAAACAATA ACACAGAGGATGGGTGCAGTGCCTGTAATCCCAGCACTTTGGAGCCTGG 25 GGCGGGCGGATCACTTGAGGNCA

Sequence ID 365

GTCCCGGAATCGCGGCCGCGTCGACCTTTTCTATGCCTGCTATATAAACAGTACCT
TGCAAGATGTCCTGTCTGATATCCACAAAGGGGTATTGTCAACCCCAAGTTCAGAC

AGCTTTGTATTCTTCTGTCCCTGGATACATGAATTACTGCCATCTTTACACAGCGC
CCTAAAATACCAACGCGAAGTTACCTGCTCAGCTTGAAGCTGCGCTGTACCCTGGA
ACCAGCACTTCTGCTGAATGACTCAGGATGAAGCCTCGACTTCTCCCATCCC
ATGCCCAGACCCCAGTGGCTCCTTTCCCAATCTGATCCAGTGACTTTAAGTCCAGC
TGTTGCAACCTGGGCATGAGGAGGAGTGCAAGATGGCTTTGTCCTACCTGGAAAGA

35
GGCTTTCTGGA

- 136 -

Sequence ID - 368

nt: 329

10 AGAAATACAAACTACCATCAGAGAACACTATAAACACCTCTATGCAAAT

Sequence ID 369

20

30

35

15

Sequence ID 370

25 TTTTAAAAAGATCAACA

Sequence ID 371

- 137 -

Sequence ID 373

CCAGTGTGCTGGGATTACAGGCATGAGCCCTGCACCCAGCCTCTTAAACTGATCAT
ATGATATTGGTTCTCAACCAAGGGTGACTTTGCCCCCAGAGGATACTTGGCAATGT
CTGGAGATACTCAGTTGTCATGACTTGGACAGGTGCTACTGTCACCCAGTGGGTAG
AGGTCAGGGATGGTGCTAAACATAGGACAGCTGTCAAGAGAAAAGAATGTACCCAG
CCCCAAATGTCAGTAGGGCTGAGGTTGAGAAACCCAGCTGTAGCTGACGTGTGAAG
GACAGACTGGCCTGGAAGTGTTTTCTGCCCCTTTCCACCCCTGCATATTAGTTA
AGGCCAAAGGAAAAAAGGAATGCAGGAAATGCCCGTTAAAAATCTTCAAAACAATA
TAAAATGATCAATTCCACTAAAACCCTTTACACATTTAAGTATAAAGGTATTGGTA
GGAAAATTTGTTATTCACTGCTTTTCTCAGTGTCATGAAATAATTATTTCTGCTGT
CAGTTT

Sequence ID 374

20

25

35

15

5

10

CGCTTCGAGAGATTCGTCGTTATCAGAAGTCGACCGAGCTGCTCATCCGGAAGCTGCCCTTCCAGAGGTTGGTGAGGGANATCGCCCAGG

30 Sequence ID 380

CTAAATCTTCAACCACAAAAAGGTTTTTATTTGTATTAAGATGTTACCACTTTTGA

- 138 -

CAAAAAGCTTAAAATATTTTATATTTCAAAGGAAAATTAGCAACATAACTTTACAA TATATTCTATGATATTTTGATTGTGAGGGCTACTCTATTTAAAACTGATGATCTCT GTTGTGTTGCTCAGATGCAGGAAAGCAGCAAAA

5 Sequence ID - 381 nt: 534 GACTTANATCTAAATGGACCACATTCTCTACTTAAAAAAATGCTATTAACCATGTG ATCTTCTCAGTCATGAGGTAATCTGGTGACTACCCTTCCTCAAAGCCAGTTGGGAT ATTCTTTGAATAGAGTAAAACAGTGTTTCTAGGCTGGGAGACACCCAGACATAGTTG AGGACAGAGGTGCTAGAAAATAGGAAGTTTAAAAGCATGTGCGGTGATGCTCAGAG 10 GAGGTAAACCCCACCCTCATGCTCATAGCTTCCAATCATTTTCTCTAGTTCTTAAC TCTTAAATGTGAGAAATGCTTGAAGATTCTAGTCATCTGAAGAAAGTCTCTTTATT AAAGATTTTCATAAAAGAGACCAAAGCAGACAAACAGAAAAAGACATCTTGGGGAA AAAAACAAGGATAATGGGAAGAAGGAAAGTTTTAAAAATTATCAATATCCTCAG 15 AGCAAAACAAGCTCCTAAAAATAAAGTTTG

20

25

- 139 -

### TTGGTA

5

10

Sequence ID 384

### Sequence ID 386

25

30

35

### Sequence ID 387

### CTTTTTCTTTAATAA

Sequence ID 388

CTTTGGACACTAGGAAAAACCTTGTAGAGAGAGTAAAAATTTAACACCCATAGT 5 AGGCCTAAAAGCAGCCACCAATTAAGAAAGCGTTCAAGCTCAACACCCACTACCTA AAAAATCCCAAACATATAACTGAACTCCTCACACCCAATTGGACCAATCTATCACC CTATAGAAGAACTAATGTTAGTATAAGTAACATGAAAACATTCTCCTCCGCATAAG CCTGCGTCAGATTAAAACACTGAACTGACAATTAACAGCCCAATATCTACAATCAA CCAACAAGTCATTATTACCCTCACTGTCAACCCAACACAGGCATGCTCATAAGGAA AGGTTAAAAAAGTAAAAGGAACTCGGCAAATCTTACCCGCCTGTTTACCAAAAA 10 CATCACCTCTAGCATCACCAGTATTAGAGGCACCGCCTGCCCAGTGACACATGTTT AACGGCCGCGGTACCCTAACCGTGCAAAGGTAGCATAATCACTTGTTCCTTAATTA GGGACCTGTATGAATGGCTCCACGAGGGTTCAGCTGTCTCTTACTTTTAACCAGTG AAATTGACCTGCCCGTGAAGAGGCGGGCATAACACAGCAAGACGAGAAGACCCTAT 15 GGAGCTTTAATTTAATGCAAACAGTCCTAACAAACCCCAGGTCCTAAACTCCA AACCTGCATTAAA

Sequence ID 389

- 141 -

AGAGCAAGAGACTTCTCAACTGGAAAAGGATAAGAACAATTGGAGAAGGAAAATA AGAGACTCCGACANCAAGCAGAAATTAAAGATCCACATTTGAAGAAAATAATGTGA AGATTGGAAAATTTGGAAAA

5 Sequence ID - 391 nt: 566 CTTTGAAGAACTTTGCCAAATACTTTCTTACCAATCTCATGAGGAGAGGGAACATG  ${\tt ATCAAGAAACCAGACTGTGATGACTGGGAGAGCGGGCTGAATGCAATGGAGTGTGC}$ ATTACATTTGGAAAAAATGTGAATCAGTCACTACTGGAACTGCACAAACTGGCCA CTGACAAAAATGACCCCCATTTGTGTGACTTCATTGAGACACATTACCTGAATGAG 10 CAGGTGAAAGCCATCAAAGAATTGGGTGACCACGTGACCAACTTGCGCAAGATGGG AGCGCCCGAATCTGGCTTGGCGGAATATCTCTTTGACAAGCACACCCTGGGAGACA GTGATAATGAAAGCTAAGCCTCGGGCTAATTTCCCCATAGCCGTGGGGTGACTTCC  $\tt CTGGTCACCAAGGCAGTGCATGCATGTTGGGGTTTCCTTTACCTTTTCTATAAGTT$ GTACCAAAACATCCACTTAAGTTCTTTGATTTGTCCATTCCTTCAAATAAAGAAAT 15 TTGGTA

Sequence ID 394

Sequence ID 395

35

30

35

- 142 -

TATTTTTAAAAAACTGACCCTATTCTCAGGATGAAAATAATACACTAGTAATAGTC
TGCTCTGTTGGTTAACTCCTCGTAAGGAGGTCAATTAAAATGCTGTAGTGTTGCAA
GGGAAGGAGGAGGAAGCATCATATTCCTTCACTAGCAGGATCAAGAAAGCTTTTATA
GAAATATACAAAATCTTCACTTCTTGAAGGATTGGTAAAATTTAATAGCCAACATT
GGGCACTTATTCATTCTCTGAGTAAATATTTATTGCAT

Sequence ID - 397 nt: 534

20 GACCCGGAATCGCGGCCGCGTCGACGGAAGCTCCTGCCCCTCCTAAAGCTGAAGCC
AAAGCGAAGGCTTTAAAGGCCAAGAAGGCAGTGTTGAAAGGTGTCCACAGCCACAA
AAAGAAGGAGATCCGCACGTCACCCACCTTCCGGCGGCCGAAGAACAAGCTTGACCAC
GGAGACAGCCCAAATATCCTCGGAAGAGCGCTCCCAGGAGAAACAAGCTTGACCAC
TATGCTATCATCAAGTTTCCGCTGACCACTGAGTCTGCCATGAAGAAGATAGAAGA

25 CAACAACACACTTGTGTTCATTGTGGATGTTAAAGCCAACAAGCACCAGATTAAAC
AGGCTGTGAAGAAGACTGTATGACATTGATGTGGCCAAGGTCAACACCCTGATTCGG
CCTGATGGAGAAAAAGCACATATGTTCGACTGCTCCTGATTACGATGTTTGGA
TGTTGCCAACAAAATTGGGATCATTTAAACTGAGTCCAGCTGCCTAATTCTGAATA

- 143 -

CAGCCTCCTGCCTACCCCAAGATGCCCCTCCCCACCCTGACCGTGCTAACTGTGTG
TACATATATATTCTACATATATGTATATTAAAACTGCACTGCCATGTCTGCCCTTT
TTTGTGGTGTCTAGCATTAACTTATTGTCTAGGCCAAAGCGGGGGTGGGAGGGGAA
TGCCACAG

5

25

35

20 Sequence ID 400

30 Sequence ID 401

GAAGCCAAACCAAAGGGAGCTTCTACTTCATGATGCCATTTATGTAAAGTTCAGGC
AGAGAAAATCAGTGGTTTAAGAAGTTAGAAATAATGATTATCTTTGGAGGGATTGCA
ACTGGAAGAAGTCATGATTGGGATTTCTGGGTCCTAATAGTGCTCTGTGTCTTGAT
CTGAGTGCCGACTACATGAGTGGTTAGGTTTGCAAAATTCATTGAGTTATGCACTT
AATGGTGTTGTCTTATTAGAGCTGATGGAGGAGAGAGGGCCTTCAATTTGCACAACT
GAGTAATCAGCTAGGCCCAGTCACTAGGTGAACAACTTACTGCTACCAATCAGCCT
TAGAGCAGGAATCAAACTCATGTCTCAGAAAAGTTATTAATTCAGCTTGTCTTGGG

### - 144 -

ACTTCCTTCAGAGTCACTCTTGAATAGCTGAAATAGTAAATGTTAAATCTGTGGAT GCAAGTGTGTAAATTATTTTAGTCATCAGCTCTAATAAGATGGCCTTTGGGGAAAT GAGTATAAGGTCACGAAAATGAAATGGCAAGAAGGAGGTCTACTATTTCTTCTGTA ATACTGATTTTTACCCCATCAGGGTCAGTCCCCAAAGGTTGTAAATGTGAAGCTTG GTCTTTTTCTTTA

Sequence ID 402

GACCCTATTCTCAGGATGAAAATAATACACTAGTAATAGTCTGCTCTGTTGGTTAA  $\tt CTCCTCGTAAGGAGGTACAATTAAAATGCTGTAGTGTTGCAAGGGAAGGAGGAAA$ GAATCATATTCCTTCACTAGCAGGATCAAGAAAGCTTTTATAGAAATATACAAAAT CTTCACTTCTTGAAGGATTGGTAAAATTTAATAGCCAACATTGGGCACTTATTCAT TCTCTGAGTAAATATTTATTGCATGCTTATCTTGTATCAACATTGNGATGAAAGCN CAAGAATGAAAGAGGGGGGGAGAATGTTTANAGAATAAGGCTGAAACACAGATTTTG TAGGGAGCGTAGGGGAGACTGANAAAACAG

15

25

30

10

5

Sequence ID 403

AAGACACCTGATAGATTGTCTTGTATTATTTTTTCCTTTGCCTTCTTACAATCTCAG TGATTAGAATTGGGCTGAAAACAATACATCAAATTCTCAGCAAAATCCTTATGGGT TGCTGGATACCGAGGGTTTTTAAGATCTTTAGACTTCACTATATAGAACAAATGTT GAATGGGAATTTTCTTTATTTCTATANCGTTTNG

20

Sequence ID 405

 ${\tt CCCGGAATCGCGGCCGCGTCGACGATGAGCATTTTTTCATGTGTCTTTTGGCTGCA}$  ${\tt TAAATGTCTTTTGAGAAGTGTCGGTTCATATCCTTTGCCCACTTTTTGATGGG}$ GTTGTTTTTTTTCTTGTAAATTTGTTTGAGTTCATTGTAGATTCTGGATATTAGCCC  ${\tt TTTGTCAGATGAGTAGGTTGCGAAAATTTTCTCCCATTTTGTAGGTTGCCTGTTCA}$  $\tt CTCTGATGGTAGTTTCATTTGCTGTGCAGAAGCTCTTTAGTTTAATTAGATCCCAT$  ${\tt TTGTCAATTTTGGCTTTTGTTGCCATTGCTTTTTGGTGTTTTAGACTTGAAGTCCTT}$ GCCCATGCCTATGTCCTGAATGGTAATGCCTAGGTTTTCTTCTAGGGTTTTGATGG TTTTAGGTCTAACGTTTCAGTCTTTAATCCATCTTTTAAAAGTCTCTTCACAGTAC ATGAGTAGTAGTGACACCAATAATGTCAGAGCAGGGAACTCCCAGGTTCTGCCCAT  $\tt CCACAAAAACAACAATAAGCTGGCAAAAACTTTAAGAATCAACTTTTGCAGATCT$  $\tt CTGAAATCTAGTCAAAACTTAAACAGAGGAAAGATTAATAAAGACNGGCTGCCTGA$ GATAACACTAACACAC

35

Sequence ID 406 CATCAAATAAATAAATAAATTTTAAAAGTCACAGCATTGAATTTTTAAATGT

10

30

35

TTGGGATGATAAAGCACCTGCTTATCATGAAGCTANAGAAATTCAATGACACGTTT
GCCAGGGTCTTTGCTAGTGATGTTGGAACAAGTCTGTAATGCTGATGAAACATCAC
TGTTCGGGCATTATTGCCCCAGAAAGACACTGACTGCAGCTGATGAAACAGCCCTT
CCAAGAATTAAGGATGCCAAAGACCAAATAACTGTGCTGAGATATACTTACGCAGC
AGGCATGCATAAGTGTAAACTTGCTGTTATAAGCAAAAGCTTGCGTTCTCACTGTT
TTCAAGGAGTGAATTTCATACCAATCCATTATTATGCTAATAAAAAGGCATGGATC
ACCAGGGACATCTTTTCAGATTGGTTTCACAAACATTTTTGTACCAGCAGCTTGTGC
TTACTGCAGGGAAGCTGACTGGATGATGACTGCAAGATTTTTTATCTTAACAA
CTGTTGTGCTCATCCTCCAGCTGAAATTCTCATCAAAAATAATGTTTATGGCTCAC
ACCTGTAATCTCAACACTTTGGGAGGATTGCCTGACCCAGGAGTTCAAGCCCACCC
TGGGCAACACACAGCAAGACCCAACCTNTC

Sequence ID 407

## Sequence ID 408

CCATCTCCAAATTTAGTATTCATTCTGTTTAGCATATTATCAGTTGCCATCTATTT
GTTTTAACTGATTACTTGAATCTGATTAAACATCACAGAAATGGGCTTTGATAAGA
ACAATATTGAATAAGAAATTTTAAATAACAAAACAGCTTATAGAAAAATTCAGCAT
AACTTTTCCATCACCTTCACCACCCTTGCCTTTTATTATCCTGTCCTGTATCACTG
CTTTCTGTTAGCAGTGTTGTGTGAGTTAGGATTTGGGCAGGAAAGCAAAACCACC
ACCCGTCATTTTCCCAGAATGAAGGGTTTGACGTAGGATGTAGACTTTGTATAGTA
GTTGGGAGAGCTGTGGGGAGTGAAGGTCAGGGATGTCACCTACAGAAGTCAGGGAAT
CTGCCACCAGAGATCCTGCATCAGAAACAGCCAACAGCGTGCTTCTGAAGAACTAG
TGGGGAAGTGGCTATAATTCTTAGGAATCCCAGCAAGTCCGCACCACTGTCTCAGT
CTACAGCAGTGGAGAAAGGGGTTTCCAGGAGCTCTCTGGAAAAGTTCCTGCCCACAC

- 146 -

TTTGCAACAATCTTCAGAGGATAATGGGCTTCTCTTCCAGCTTCCACACCCAACAA GAGTGCCTTTCATCGGCCAACTCTAACCTGGAACCCTATGGCAGAGGGGATTTAGG AGACAGTTTGTNATGTCTGTGGAATGCAAATGAANANGTANCAATGCTTANTTGAC AGCGGNCATACACAAATNTNGAAA

5

Sequence ID 409 GATCCGTNGACT

Sequence ID 410

10 CTCTTCCCAGCCCCTGAGCCCAGCCCCTTCCCAAGTGGTGCCAGACAAAAAACTAC ATGGCCCTTTCGTGTCTTGGGGGTGGAAAGGGAGGGATGAATTGGGGTGATAGAAC CCTGGTGAATTCAGAGTAATCTTTCTTTAGAAAACTGGTGTTTTCTAAAGAAACAG GATAGGAGTTTAGAGAAGGCACCAAAGCTTTCACTTTGGTTTGGCACCAGTTTCTA ACCATCTGTTTTTCTACCCTAGCTATCTTTTATTGGTAAAATATAAATGTATAAT 15 AATTTTTGATTCTCCATTTTCCAAAAGTAAGAGACTCCAGCATGGCCTTCTGTTTG CCCCGCAGTAAAGTAACTTCCATATAAAATGGTATTTGAAAGTGAGAGTTCATGAC AACAGACCGTTTTCCATTTCATCTGTATTTTATCTCCGTGACTCCACTTGTGGGTT T

20

25

30

35

505 nt: Sequence ID - 411 TGGAGCTGAAAAATTCCTATTACCTAGGGGCATCACAACGCATTGCATTTCGCCCG TGTTTGGGATGATGCTGGTGTAAACCTACTATGCTGCCAGTCATGTAAAAGTATAG CACACACAATTAGTAGGTAATGCTTGCAAATAATAATGAAAGACTCTGCTACTGGT TTATGTATTTACTATGCTATACTTTTTGTCATTACTTTAGAGTGTACTCCTACTTT TTTTTTTTTTTTTTGAGATGGAGTTTCACTCTTGTCCTGTAGGCTGGAGCGAAN TGGCGCGATCTCGGCTTACTGCAACCTCCACCTCCTGGGTTCAAGCGATTCTCCTG TTTGTATTTTTGGTAGAGACAGGGTTTCACCATGTTGGCCAGGCTGGTCACCAACT CCTGACCTCAGGTGACCCGCCTCCTCACCTCCAGAGTGTTGGGATTACAGGNGTGA G

Sequence ID 412

ATAAAAATTAGCTGGGGGTGATGGGCCCTGTACCCCAGCTACTCGGGAGGTGAGGT AGGAGAATCACTTGAACCCGGGAGATGGAGGTTGCAGTGAGCCAAGATCGTGCCAC TAATAATAATAAAAGGAATAACATAGCTAGGAATAAATTTAATCAAAGAGGTGAA

- 147 -

Sequence ID 413

20

25

30

35

5

Sequence ID - 415

596

nt:

- 148 -

### Sequence ID 416

5

- CTGGTGGCGGCGGTCGTGCGGACGCAAACATGCAGATCTTTGTGAAGACCCTCACT
  GGCAAAACCATCACCCTTGAGGTCGAGCCCAGTGACACCATTGAGAATGTCAAAGC
  CAAAATTCAAGACAAGGAGGGTATCCCACCTGACCAGCAGCGTCTGATATTTGCCG
  GCAAACAGCTGGAGGATGGCCGCACTCTCTCAGACTACAACATCCAGAAAGAGTCC
  ACCCTGCACCTGGTGTTGCGCCTGCGAGGTGGCATTATTGAGCCTTCTCTCCGCCA
  GCTTGCCCAGAAATACAACTGCGACAAGATGATCTGCCGCAAGTGCTATGCTCGCC
  TTCACCCTCGTGCTGTCAACTGCCGCAAGAAGAAGTGTGTCACCCAACAACCTG
  CGTCCCAAGAAGAAGAAGTTGTTCTTTCCTTGAAGGGCAGCCTCCTGC
  CCAGGCCCCGTGGCCCTGGAGCCTCAATAAAGTGTCCCTTTCATTGACTGGAGCAG

## Sequence ID 418

#### - 149 -

# CACTGACTTGAGACCAGTTGAATAAAAGTGCACACCTTATAAAAAA

# Sequence ID 419

## 10 Sequence ID 420

5

15

20

25

30

Sequence ID 421

## Sequence ID 422

TTA

10

CTTGGCTCCTGTCCATGTACTTGGGGCCCATGAGCTCTGCAGGGACCTTGGAAAGAN
AGAGACGGGTGTTANGGCANGGGAAGGCATTGTCTTCAAACAGGAAAAAGCTGA
NAATGGAAACAGGCGAAACTTACCAAGTGTAACATCACCTGGAACTGAAGGAGGGT
GGGAAGGTTTTAATTATTTTAAAAAATAGAGATGGGGTCTCACTATGTTGCCCAGGC
TGGTCTCAAACTACTGGGCTCAAGTGAACCTCCTTCT

Sequence ID - 423 nt: 387

TGTTTCTCNAGGGCGAGAGGCTGTCTTANAGCACCATTCTCTGGCCCTNGTCCCAT
GAGAAGGAACCGCACTCAGGAGCCACACTCTCCCACTNCCCTTGCCCANAAGACTC
ACAGAGGGCACGGAGCTGGCTGTGGTGAGAGAGGTCCANCAAATTCCTGTCTGCA
NAAGGGTTCTGAACACCACCGCCTGGCAGCGTGCTGGAGGAGGATTCCTCTTTTC
CTCACAGCAATTCTGACCAGAAACCTGTCAAATCAGGAATGGCTAAAATAAGACCA
GGGTATGAATGACCATCAGCCACAGTAAAACCAAGGCACAGCTCTCCTGAGCCCAC

15 Sequence ID - 424

nt: 420

CGCAGAATGGCTCCCGCAAAGAAGGGTGGCGAGAAGAAAAAGGGCCGTTCTGCCAT
CAACGAAGTGGTAACCCGAGAATACACCATCAACATTCACAAGCGCATCCATGGAG
TGGGCTTCAAGAAGCGTGCACCTCGGGCACTCAAAGAGATTCGGAAATTTGCCATG
AAGGAGATGGGAACTCCAGATGTGCGCATTGACACCAGGCTCAACAAAGCTGTCTG
GGCCAAAGGAATAAGGAATGTGCCATACCGAATCCGTGTGCGGCTGTCCAGAAAAC
GTAATGAGGATGAAGATTCACCAAATAAGCTATATACTTTGGTTACCTATGTACCT
GTTACCACTTTCAAAAAATCTACAGACAGTCAATGTGGATGAGAACTAATCGCTGAT
CGTCAGATCAAATAAAGTTATAAAATTG

25

30

35

20

Sequence ID 425

GGAAACTGATGCCAGTCAGAAACTCAGATCAAATGAAGGGGTGAAGAAGACCAGAA
TTGATCTCTCTGTAGGAGAATATAAATGACTTTTTTAAAGTACATATTTTCTGTGA
AAGACAGTTTTTTGTTTAATGCAAAAATGTTAACAATGTTTATATCATGTAGAAGT
AAAAGATCGTGAAACAGCACAGAGAACAGTAGTAAGACAGATTGAATTGCACTGTT
GTAAGATGATGAACTTACAATATTAAGTGAAGGTAGACTGTGATAGATTAAGGATA
TATATTGTAATCCCTAGAGCAATTGTCAAAGTGGTACAGGTAAAAAAGCCAATAGAG
GTGATAAAATGGAATACTAAAAAAATATCAGATGAATAATAAAGAAGACAGGAAATG
AGGAACAGTGGAACAGAATGAATAAAAAAACAAGACCATTAACTTAATCATTAATAA
TTACTTTAAATGGGTTAAACATTATGGTTATAAGGCAGAATTACTTTAAAGTGTATATT
AAAGAGCAAGCTCCACTATATACTGTCTACAAGAGATAAAAAAGCTTACTAGGGAA

- 151 -

GTGAAAGATCTGTACAACAAGAATTACAAAACACTGCTGAACGAAATCATAGGTGA CCA

## Sequence ID 426

- - Sequence ID 427

GAGCCCTGATTGTGCCACTCCACCTGGTTGCAGA

15

35

TTCCAATCTTCGTGTTCACTTTAAGAACACTCGTGAAACTGCTCAGGCCATCAAGG
GTATGCATATACGAAAAGCCACGAAGTATCTGAAAGATGTCACTTTACAGAAACAG

TGTGTACCATTCCGACGTTACAATGGTGGAGTTGGCAGGTGTGCGCAGGCCAAGCA
ATGGGGCTGGACACAAGGTCGGTGGCCCAAAAAGAGTGCTGAATTTTTGCTGCACA
TGCTTAAAAACGCAGAGAGATATGCTGAACTTAAGGGTTTAGATGTAGATTCTCTG
GTCATTGAGCATATCCAAGTGAACAAAGCACCTAAGATGCGCCGCCGGACCTACAG
AGCTCATGGTCGGATTAACCCATACATGAGCTCTCCCTGCCACATTGAGATGATCC

TTACGGAAAAGGAACAGATTGTTCCTAAACCAGAAGAGGAGGTTGCCCAGAAGAAA
AAGATATCCCAGAAGAAACTGAAGAAAACTTATGGCACGGGAGTAAATTCA
GCATTAAAATAAATGTAATTAAAAGG

# 30 Sequence ID 428

TGCAGGATCCGTCGACTCTAGATAACATGGCTAGAAAAGAGAATGAAAAAGTTGGA
ATTTTAATTGCCATGGTATGGGGGGGTAATCAGGTTTTCTCTTATACTGCCAACAA
AGAAATTAGAACAGATGACCTTTGCTTGGATGTTTCCAAACTTAATGGCCCAGTTA
CAATGCTCAAATGCCACCACCTAAAAGGCAACCAACTCTGGGAGTATGACCCAGTG
AAATTAACCCTGCAGCATGTGAACAGTAATCAGTGCCTGGATAAAGCCACAGAAGA
GGATAGCCAGGTGCCCAGCATTAGAGACTGCAATGGAAGTCGGTCCCAGCAGTGGC
TTCTTCGAAACGTCACCCTGCCAGAAATATTCTGAGACCAAATTT

- 152 -

Sequence ID - 429

5

10

25

30

35

ACC

nt:

535

## Sequence ID 430

#### Sequence ID 431

#### Sequence ID 432

## Sequence ID 433

## Sequence ID 434

ACCATGCTGCTANTC

TTCGGACGCAAGAAGACAGCGACAGCTGTGGCGCACTGCAAACGCGGCAATGGTCT

CATCAAGGTGAACGGGCGCCCCTGGAGATGATTGAGCCGCGCACGCTACAGTACA
AGCTGCTGGAGCCAGTTCTCCTCGGCAAGGAGCGATTTGCTGGTGTAGACATC
CGTGTCCGTGTAAAGGGTGGTCACGTGGCCCANATTTATGCTATCCGTCAGTC
CATCTCCAAAGCCCTGGTGGCCTATTACCANAAATATGTGGATGAGGCTTCCAAGA
AGGAGATCAAAGACATCCTCATCCAGTATGACCGGACCCTGCTGGTAGCTGACCCT

30 CGTCGCTGCGAGTCCAAAAAGTTTGGAGGCCCTGCTGCTCGCTACCAGAA
ATCCTACCGATAAGCCCATCGTGACTCAAAACTCACTTGTATAATAAACAGTTTTT
GAGGGATTTTAAAA

### Sequence ID 435

Sequence ID 436

20

5

Sequence ID - 438 nt: 577 GTCGACAGGGATGACATAACTATTAGTGGCAGGTTAGTTGTTGGTCACTTTCAACT  $\tt CTGGGTTCAAGCGATTCTCCTACCTCAGCCTCCCGAGTAGCTGGGATTACAGGCAT$  $\tt GCACCGCCACACCTAATTTTCTATTCTTAGTAGAGACGGGGTTTCTCCCTGTTGGT$ 25 TCCTGGAACCACAGACATGAGCCACCACGCCTGGCCCCTTTTAAAATATTTCTGCT CATTGATGATGCACCCAGTCACCCAAGTGCTCTGATGGAGATGTATAAGGAGATGA ATGCTGTTTTCATGGCTGCTAATACAACATTCATTCTGCAACCCCCAAATCAAGAA 30 GTAATTTTGACTTTCAAGTCTTATTATTTAAGAAATATATTTTGCAAGACTATAGC TGCCATAGACCGTGATTCCTCTGATGGATCAGACAAACTAAAATGAAAACCTCCTG CAACGTATTCATCATTCTAGATCCCTGAGGAATCGCCACACTGACTTNCACAATGG GTGAACTGGGTTACAGT

Sequence ID - 441 nt: 552

AAACAAAATTATTCTCTGAGAGGGAAAGGACATTTGAGGGAAACATCAAATTTCCC
CATAAATAAATGAATGGAGTTTGCAGGAAGGTGAGGGTGAGCAGAGATGTGTGGG

- 155 -

ACATCTCTGACCATCCATCGCTGTATTCAAATGGATTGTTTTATTCCATTCTGGTC
TCAGGCATGACCACGTCCAGTGAAGACATTTGAGGCAGCACATCTCAGGACCCAGG
CAATAGACTGGCCCCAACTCAGGCTGGACTAAGGTGTGATTAATTCTTTGTTTTTT
GTGTGGAACAGCTCACCTTGTCAGACAGCCTCAGGGCATCTCTGAGACACAGGGGC
AGAAAATGACATTCATCTTTTGAGTCCTCATCCATGGAGTGCTGTTTTGGGGGGC
TGCATCTGCTGAAGCGAGAACCCCATTCTGCCACCCCACCAGGATGCCCATTCTCC
AGGACTTCTCCAACTTACTATTAGACTAAAACCAGAACAAACTGTATTTA

- 10 Sequence ID - 442 nt: 606 AAAACCTAGTTGGTATTTTGCTTATTTAATACTATAGAAATATGGTGATCTCATC TTTAATAGAGTGCTTTTAAGGTCCCCAGTGATAATCTCCTAAAATCATGAACTTTA AGAATTTATAATGTTAATATGAGGAAATGAAATCTGGATTATCTCACCACATATTA 15 TATAATTCATTAGTGACAGAGCAAGAACTCCAGGTCACCTGTCTATTCCATGTTTT TCCTATCTGCCTTTAAATGTTGAGATACTACCCTTATCTCATGTGAATGGAGAAAC TGCCTAAAATGCTAAAACTGACTCAGAGGCACCCAGACATAAGTGAAGTGTGATTA GAAAATCCTGGTCAGTTGAGTCTTAGCCAAATGTGTACCTACTGTGTCTGCCTCTA 20 TCAAGTCAATGAAAACATGATCTGAGAACTGTAAGTCCATTTATGGAAAGGGTTGA TTTANAGATATTTTGAACTTNCAGTGATGAGCCCCTTCTCAAATAG
- Sequence ID 446

  CGGACTCCTGTGCTAATTGTCAGCTTACATATCATTGTATAGAGACTGTTTATTCT

  GTACCAAACTGATTTCAAAAGTACTACATNGAAAATAAACCGGTGACTGTTTTTCT

  TCATAAAGTTCTGCGTTTGGCATCTTCACTCTTTCCAAAATGTATCTGTACATCAN

  AAATGTCACTATTCCAAGTGTCTTTTTAGTGTGGCTTTAGTATGGCTTCCTTTTAA

  TATTGNACATACATTGNATCTTTGTTTTATGGNAATAAGTAATAAAAATGTAGACT

  TCATATTTTGTACAAAATGTCCTATGTACAGAATAAAAAAGTTCATAGAAACAGCC

  NANAA

- 156 -

ATAGCTAGGAATAAATTTAATCAAAGAGGTGAAAGACTTATACACTTAAAACTACA
AAAAAAAAATCACTGAAGGAATTATAGACCCAAATAAAAAATAAAATAAAAAGACATT
CTGTGTTTTAGGGAAAGAAGACTTAATATTGTTAAGATGTCAATACTACCCAAAGT
GATCTACAGATTCAACATAATCCCTATCAAAATTCCAACAGCCTACTTTGTAGAAA
TGGAAAAGCCAATTTTCAAATTCAGATGGAATTGCGAGGGGTTNTGAATAACAAAA
CACNATCTTGGGGAAAAAAAAAAAAAAAAAAAAACAAAAGTCAAAGAACTCACACTTCTNTAT
TTATAAATTTACTACAAAGTTATAGTAATCNAA

Sequence ID - 448

5

20

25

30 .

35

nt: 329

15 AGTCAAGATGAGTGGGAAACCATCTCAATAAACACATTTTGGGTTAAAA

Sequence ID 450

Sequence ID 452

- 157 -

 $\label{eq:control} \textbf{ACATAATCCTGGGAGGCAATTGGCATCATACATATTTTGCTTTGTAATCTCCTGCTTTGATTCTGACTGGGACCCAGC}$ 

Sequence ID - 453 nt: 747 GGATCTAAGACCAGCCTGGCAGCCACCAGATGGTGATTCTAGTCCTGGCTCAGTCA 5 GTAATAGGTCACTGACCCCAGAGAAATCAATTCAGCCTCCCCAGGTCCTTGGATTT CTTTCTGTGAAAATGAAAGCATAGGTAGGAATTTCCCATGGAACAGCTAGCAGAGG AGAAATATTAAAAGTCAGGAGACTCATGCTATAGTTTTCATACTTCATTACAACAA TGTTGTTTAGGACAAGTGAGTTAACCTGTTAGCTTCCTCTATATAAAATGGAAAGT 10 CATTAAAAACCTACATAGCAGGGTTCTTGTGAAGATCAAGTGATAATGTAGGAAGC ATGTACAAATGTCACATTCTGCCGTCACGTAATGGTCCTCACAGCTTGAGGTAGCA TTTAGCATGTCATGATTTAGTACAAGGGTTGGCAAACTGTTGCTCTTGGATTAA GTCTGGCTCATTGCCTGTTTTTCAAAGAAAAAATTGTATATGTGTGTATATATGT TATATATAGGTACACACACATATGTGCTATATATAGCATATATACACACATAATAT 15 ATAAACATGTACATATATAGCATTATATATATACCGTGTATAATATCTCCAGTCCT CATGACCAGCCATGCTTCATTTACATTTGCATACTCTATGATTGCTTTCATGC AACAATGGCAGAGTTGAGTGATTGTTTTGCACAGANACTGTATGGCCCACTAAACC TAAAATATTAATCTCTGCC

35

CATATCCGGGTGCGGCTCCACCCCTTCCACGTCATCCGCATCAACAAGATGTTGTC
CTGTGCTGGGGCTGACAGGCTCCAAACAGGCATGCGAGGTGCCTTTGGAAAGCCCC
AGGGCACTGTGGCCAGGGTTCACATTGGCCAAGTTATCATGTCCATCCGCACCAAG
CTGCAGAACAAGGAGCATGTGATTGAGGCCCTGCGCAGGGCCAAGTTCAAGTTTCT
GGCCGCAGAAGATCCACATCTCAAAGAAGTGGGGCTTCACCAAGTTCAATGCTGAT
GAATTTGAAGACATGGTGGCTGAAAAGCGGCTCATCCCANATGGCTGTGGGGTCAA
GTACATCCCCAATCGTGGCCCTCTGGACAAGTGGCGGCCCTGCACTCATGAAGGCT
TTCAATGTGC

TCCCGGAATCGCGGCCGCGTCGACCTTGTCCTTGAGCGTCAACCTTCTTTCCCTGA
AGTGGCTGGGGTTCCTGTTTCCTTTTGATTGACAACTTGTGTTAACCCTCGCAC
ATCTCTGGGCCAATTTTTGCTTGTAAGTCTTTCCGGAGACCCCTGGAATTTAAATC
ATTAGCACCGCGCCCTTCCCCGAAGAGTCTTCGAAGGGTTGCCGCTTTTCGGTGGC

GCAGTTCTCGCGAGAAGGTGACTTTCTTCTCGGTATTTCCTGGTTTCCAGAATCC
TTAGCGCGAGGCGGAAAAAATATTTCTCCCAGCTTGTGTTGATGCCGCGATTTTGA
CTGAGACTTCTTCCCACGATTTCTGTTTTTGCTTCCAAGGAAAATGGCAGCTCC
CGAGCAGCCGCTTGCGATATCAAGGGGATGCACGAGCTCCTCCTCGCTTTCCCCGC
CTCGGGGCGACCGAACCCTTCTGGTCAGGCACCTGCCGGCTGAGCTTACTGCTGAG

AGGAAAGAGGGCTTGCTGAAGTACTTCGGGGCTCAGTCTGTGCGGGTCCTGTCAGA
TAAGGGGCGACTGAAACATACAGCTTTTTGCCACATTCCCTAATGAAAAAGCAGCTN

TAAAGGCATTGACAAACTNCATCAACTGAAACTTTTAGTCATACTTTAATCG

- - Sequence ID 461
    TAGGAGGCTTATTCACTGATTTCCCCTATTCTCAGGCTACACCCTAGACCAAACCT

## Sequence ID 462

TCTTTATCAAGTTGAGAAAGTTCCTCCCCTCTATTCCTAGTTTGCTAAGAGTCCTT
CTATCCTATTTCTTAATGGTTTAGTAGATGACTCTGTGGTACTTTGAAGGTTGTTT
GCAGAATTTCCATGCCATAGGCAATTTACCTTTCCTTGACATTTGAAGGATTGATG
TTGGTGCCAAGTATAGAATCTTCACAGAGTCCTCCTGTAGCTTCTAAAGGTTTAGC
TTGAAAATGTTAATTGCTTAACGCTAGTAAGTGAGAGAAAAGCTGGGGATAAATT
TTGTATCTTGCTTATATTTCAGTTCCCACCTCTGTCCNGACNAAACCCCCCATATAT

#### 15 AA

5

10

### Sequence ID 463

TAGTTTACATATCCCAACCTTTAAAAATATTCCTCTTATTAGCTTTATATTCACTT
TATAGAAGTTGAGTTTTAATTAAAATTCTTGGCATCCTGAAGTATGTCACATAGCA
TGTGCTCCTTATAAATATGTTGATATCTCAGAAGACAGCATCCCGGTTTTCATTTT
ATAAAGTACCATACTTAAGAATGCTGTAATACTTATCTTTTATAACATGTTTCCTT
CGCTTTGCTTGNCTTTTATGNCATCAGTTTTAACTGTTTACTTCATTTAACAGNTT
ACATCATNCAACAGTTTACTTCATTAAACAGTAGGTGGAAAAATAGATGCCAGTCT
ATGAAAATCTTCCCCATCTATATCAAAAATACTTTCAAGGATATACTTT

25

20

615 nt: Sequence ID - 464 CGACTTTCAACCATCAAGTGAGGAATACCTTCACATAACTGAGCCTCCTCTTTAT CTCCTGACACAAATTAGAACCTTCAGAAGATGATGGTAAACCTGAGTTATTAGAA AGATTTCCAAAACAAAACCTATGGTCAAGTTTCTGGAGAAGCAATCAAGATGTTTC 30 CCACCATTAAAACACCTGAGGCTGGAACTGTTATTACAACTGCCGATGAAATTGAA TTAGAAGGTGCTACACAGTGGCCACACTCTACTTCTGCTTCTGCCACCTATGGGGT CGAGGCAGGTGTGGCTTGGCTAAGTCCACAGACTTCTGAGAGGCCCACGCTTT CTTCTTCTCCAGAAATAAACCCTGAAACTCAAGCAGCTTTAATCAGAGGGCAGGAT TCCACGATAGCAGCATCAGAACAGCAAGTGGCAGCGAGAATTCTTGATTCCAATGA 35 TCAGGCAACAGTAAACCCTGTGGAATTTAATACTGAGGGTGCAACACCCCATTTTC CCTTCTGGAGACTTCTAATGAAACANATTTCCTGATTGGCATTAATGAANAGTCA

- 160 -

Sequence ID 469

5

Sequence ID 471 TCCCGGGAATCTGCAGGATCCGTCGACT

# Sequence ID 472

GACAGTGCCCAGGGCTCTGATATGTCTNTCACANCTTGNAAAGTGTGAGACAGCTG
CCTTGTGTGGGACTGAAAGGCAAGATTTGTTCCTGCCCTTTCCCTTTGTGACTTGAA
GAACCCTGACTTTGTTTCTGCAAAGGCACCTGCATGTCTCTGTGTTCTTGTAGGCA
TAATGTGAGGAGGTGGGGANACCACCCCCACCCCCATGTCCACCATGACCCTCTTNC
CACNCTNACCTGTGCTCCCCCCAATCATNTTT

15

Sequence ID - 473 nt: 694 AAGATGAGGCTTCTGCTGCTTCTCCTAGNGGCGGCGTCTGCGATGGTCCGGAGCGA GGCCTCGGCCAATCTGGGCGGCGTGCCCAGCAAGAGATTAAAGATGCAGTACGCCA  $\tt CGGGGCCGCTGCTCAAGTTCCAGATTTGTGTTTCCTGAGGTTATAGGCGGGTGTTT$ 20 GAGGAGTACATGCGGGTTATTAGCCAGCGGTACCCAGACATCCGCATTGAAGGAGA GAATTACCTCCCTCAACCAATATATAGACACATAGCATCTTTCCTGTCAGTCTTCA AACTAGTATTAATAGGCTTAATAATTGTTGGCAAGGATCCTTTTGCTTTTGGC ${\tt ATGCAAGCTCCTAGCATCTGGCAGTGGGGCCCAAGAAATAAGGTTTATGCATGTAT}$  ${\tt GATGGTTTCTTGAGCAACATGATTGAGAACCAGTGTATGTCAACAGGTGCAT}$ 25  ${\tt TTGAGATAACTTTAAATGATGTACCTGTGTGTGTCTAAGCTGGAATCTGGTCACCTT}$ CCATCCATGCAACAACTTGTTCAAATTCTTGACAATGAAATGAAACTCAATGTGCA TATGGGATTCAATCCCCACCATCGATCATAGCACCCCCTATCAGCACTGNAAACTC TTTTGCATTAAGGGATCATTGC

30

35

- 161 -

Α

20

Sequence ID 475

5 CATAATAAAAACAATCAACAAACAGGGAATGGAAAGAACTTCCTCAGCATGGTG
AAGGCCACATATGAAAATCCCACAGCTAACATCATACTCAATGATGAAAGACTGAA
AGCTTTTCTCCTGAGATCAGGAACAAGACAAAGATGTCACCTTTTGTCACTTCTAT
TCAACTCATTATTGGAAGTTTTTGCCAGAGCAATTAGGTAAG

- 10 Sequence ID 476 nt: 476

  CAGAATCTTTCATAGGCTGAATGTTGCTCCACAATGTGTCCTTTGACTATCTCTG

  GCTAATTATTATTTTAATCTCTTCTCAGCTTTTCCAAGAACATAACGTTAACCAAA

  GATCTTAGGCCATTCACAACTCTTTTGTAAAAATTAATGTGGATGTGAAACGAGGC

  AACAAATCCTGAAGTAGAAAGTTATTCCTGGCCAGGCACGGTGGCTCACGCCTGTA

  ATCCTGGCACTTTGGGAGGCCGAGGTGGTGATCATGAGACAGAGATCGAGAC

  CATCCTGGCCAACATGATGAAAACCCCATCTCTACTAAAATACAAAAAATTAGCTGG

  GCATGGTGACGCGTGCCTGTAGTCCCAGTTACTCGGGAGGCTGAGGCAGGGAATT

  GCTTGAACCTCGGAGGTGGAGGTTGCAGTGCCGAGATCACGCTACTCCC

  AGCCTGGCAACAGAGCAAGACTCCATCT
  - Sequence ID 477

    AAACAGAAAGTTTCTTCTAAAGGCATGATTCAGTTAAGTCATTCTTAAGTGTTAAA

    AAATTGTGAAAAATGTGCCTGTAATCCCAACACTTTGGGAGGCCGAGGCAGGA

    TCACGAGGTCAGGAGATCAAGACCATCCTGGCTAACAAGGTGAAACCCCGTCTCTA

    CGAAAAATACCAAAAACATTAGCCGGGCGTGGTTGTGGGCGCCTGTAGTCCCAGCT

    ACTTGAGAGGCTGAGGCAGGAGAATG

- 162 -

## CAGCCCATGGTACTGCCAG

Sequence ID 479

CATCAGTCTGTTATCCATGCTGACTTTCCGAAGACTTGCAGCTACTGCATTGATAT
CTTTCCTGCCAATAAGCAAAGTGTTGAACACTTCACAAAATATTTTACTGAGGCAG
GCTTGAAAGAGCTTTCAGAATATGTTCGGAATCAGCAAACCATCGGAGCTCGTAAG
GAGCTCCAGAAAGAACTTCAAGAACAGATGTCCCGTGGTGATCCATTTAAGGATAT
AATTTTATATGTCAAGGAGGAGATGAAAAAAAACAACATCCCAGAGCCAGTTGTCA
TCGGAATAGTCTGGTCAAGTGTAATGAGCACTGTGGAATGGAACAAAAAAAGAGGAG
CTTGTAGCAGAGCAAGCCATCAAGCACTTGAAGCAATACAGCCCTCTACTTGCTGC
CTTTACTACTCAAGGTCAGTCTGAAGCTGTCANAAAA

## Sequence ID 481

20

5

. 10

25

30

35

Sequence ID 483

- 163 -

Sequence ID 484

5

25

TTTTTTTTTTTTTTATTCTATTAAAAAATGTTNNTGAAAAAAGATACTTAAATTTTAA
AGATAACTNAATTCCTAANGATTTAAAATAATCCAAGCAGAGATGAAAGANCAAAT
GCAAATGCNTAAAAAGACCCCCANAGCATTGTTAGCAAAAAGCAAATATAGTTAGCC
AAGCATATATATNTCATAAAAGCAATAANAAGGCNTAAAGCAAGTTTGGGGAGAGC
TTATTTAAAACTTGTAAAAATCATTTGAATTTTTAAAAGTTTTCAAAC

TTTGGAACACAAAGTTCCCTTTTTAGAAGAATAGGTATTGAGCCCTTGAGCGTGGG

TAGAAAGATAGAGACAGAGTGATTTGCAAAATAATGGAGGATCATATTTATATATG
AATTTTCACTTATTTGAACTTTCAGATATCANCTTNAAAANCTTTGGTTTAAGTAA
AGTNTNTTAATGAGACTCCTTGGATGAAAGTAACCAAAACCAGTAAAAATAAGGTA
ATAAGGATGTAATAGTTTCTTATGGACACTCAACAGCTAGAATGCAGTTAGTCTCA
GAAAAGAATTAGAACAAATAACTGGAAGGCCATCAGGAGTCCAAAACCATCACTCT
TTTATATTTTATATTTTTTTCTCTCTTCANATGAGCATTCTCTTTCTATGTCC
ATATGGTANAAGGCGGCAGCTCCATAGATTATGGCTTCAGATGTTACAGTTCCGCT
NAATGCAGGGACAGACTTGCTATCTTTCAGTCCCCTTTCCAATCT

Sequence ID 489

TTAACAGCTGCATAGAGTTTTAAAAGTACATTATATTTTGTCAGACAAGTAAAATA

TCTGTTTTTCACGCAAAAAAAAGCCATGAAATACGTAATTTTTTAAAGACAAAAAAT

CATCTTTGAGTTTGCTCTTTGGTTTTTCTTCATTCCTTTTGAGGATTGGGAAAAC
AGAAAGATTCTTTGATTTGGGTAATGAAGAGGTAATTTGGGACAGTGTGGTGGTAC
CAGGAAGAAAGAGGATTGGAAAGGCCAGTACTGTTTTAGTTGCTCGGCACTGTTGG
TTTTGTTTTAATGTGGTTGCCCTGTCCACTACATGGTTCTATCAGTAGTGTAATCC
ATTTCAATGTAAAGCTCTTTTAGTTTTTTGTCATAGACATAAATTAATATTTTGAG
AGGCATCCCTCACCTGTTCATTTCTTCTGTGTTGAAATGAAGTACTTAAAATTACC
GTTATACATGAACTTTGTGGACTGTAAGATTTGTTATATATGTTCAAATGCCTTTT
AGCTGGCTTTTTAATTAATATGCCTGTTTTGAGTGCTTAATACAATGTAATGNGGA
TTGTAAATCATACCTATTTTAAATCATTCCTTCCTGTATATTTTGNACTCAGAGAGC
CTTATTTTATTCTTCCAGC

Sequence ID - 491

nt: 382

20

25

30

35

5

10

15

Sequence ID 492

Sequence ID 493

TGGGAATCATAATTNGTTAACTGAAGCTNATAAGATGAGAGCATTCANAGAGAAAA GAACGGAAAGATTGAATATCAGTTTCCCTTCTTTAAAAAAATTGTGGATATGTGAT CTAGCTTCTTGAGCATCACAGTGACTGATTGGCTCGTGGTAATTGATCGCTATGCT GACAATCTTATCTCCACCTATGTCATTCAATTTCTAAGAGGCAAAATCCTTAATC AGGAGGAGAGTTTAGCTCTAGCTAAATTTCCCATGCACGCATGCTCCTGCTCCCC

WO 2004/046382

Sequence ID 494

20

5

Sequence ID 495

Sequence ID 496

Sequence ID 497

GAAGACCTCACATCTGAGAGCTCATCTGCGTTGGCATTCTGGAGAACGCCCTTTTG
TTTGTAACTGGATGTACTGTGGTAAAAGATTTACTCGAAGTGATGAATTACAGAGG
CACAGAAGAACACATACAGGTGAGAAGAAATTTGTTTGTCCAGAATGTTCAAAACG

CTTTATGANAAGTGACCACCTTGCCAAACATATTAAAACACCACCAGAATAAAAAAG
GTATTCACTCTANCAGTACAGTGCTGGCATCTTGTGGAAGCTGCGCGAGATGATACT
TTGATTACTGCAGGAGGAACAACGCTTATCCTTGCAAATATTCAACAAGGTTCTGT
TTCAGGGATAGGAACTGTTAATACTTCCGCCACCAGCAATCAAGATATCCTTACCA
ACACTGAAATACCTTTACAGCTTGTCACAGTTTCTGGAAATGAGACAATGGGAGTA
AATATTACACAAATACTTATTCATTGNGGTTATTTTTATACAGTAGTGAGAAGAAT
ATTGTTCCTAAGTTCTTAGATATCTTTTTTTGGATGTGCAAAAATTTTTTGGATTGA
CAGTAACTTGGGTATACATGACACTGAAATGCCTTACTTTGGATGA

10

25

#### 20 Sequence ID 505

- 168 -

Sequence ID 508

Sequence ID - 509 nt: 575

10

30

35

5

Sequence ID 512

25 Sequence ID 513

- 170 -

Sequence ID 515
CCTGGATGACAGCATATCTGTTTATAGCTCAGTTTACTGAATACTTTAAGCCCACT
GTTGAAACCTGCT

- Sequence ID 519

  CTGCGATNGAGTTTTGAGAGGAAGGANTAAAGTNCTCATCTCNGACGGTGAGAAAG

  ATCATNACTAAGGAAACGCAGGGTTGGAAGCAGTGCTGANTGTCCAGTTTGAGTTTC

  ATGANCAAACATTTGCTGTGGGACCAGTTTTCATGGNGGTTTGTCATTTTGTCCAG

  CTGCCTGGAGCTGCTTGGTTGAAGGCACAGAATAATCAGGATTAATTGTTNAACTT

  GTATGAATTTCTTTATTTTAAAATAGGAATAATATCTGCCTTGGGAGCAAGTTGTA

  AGAGTTAACTGAAAGCTTNAGGAAAAACTTTCCCTTGCTATTTAAGTAGGGCTTTA

  CAAGTTACAATTCTATCACAGTTTTAAGATTATAAAC
- Sequence ID 521
  GCGGCGCANCTGCGGATCCANAAGGNCATAAACGANCNGAACCTGCCCAANNCGTG
  TGATATCACCTTCTNAGATCCAGACNACCTCCTCAACTTCAAGCTGGTCATCTGTC
  CTGATGAGGGCTTCNACAAGAGTGGGAAGTTTGTCTCAAAAAA
- Sequence ID 523 nt: 585

  GATTTACTGTGGGAATTTGCTCATGCAATTATGGAAACCTAGAAGTCCCATAATAT

  GCCATCTTCAAGCTGGAATCCCAGGAAAGCAGGTGGTGTAATTCTGAGATTGAAGT

  CTTGAGAACCGGGGGAGTCAATGGTGTAACTCCCAATCTAGGGCTTAAGGCCCAAG

  GACCAGGGCTGCTGGTGTCAGATGCAAATCCTGGAGTTCAAAGGATTGAGAACCA

  35 GGAGCTCTGGTGTCTGAGGGCAGTAGAAGATGTTCCAGCTCAAGAAGGGAAA

  GTAAGAATCCGTCCTTCCTCCACTTTTTTGTTCTATTCAGATGAGCCCTCAATGGA

  CTGAACGATGCTCACCCACACTGTGAGGGCTGGTCTTCTTTATTCAATCCACTGAC

5

10

Sequence ID 524

15 ATTTTG

Sequence ID 525

25

20

- 172 -

Sequence ID 527

10 Sequence 529; 660nt GACAGCAGAGCACAAGCTTNTAGGACAAGAGCCAGGAAGAAACCACCGGAAGGA  ${\tt ACCATCTCACTGTGTGTAAACATGACTTCCAAGCTGGCCGTGGCTCTCTTGGCAGC}$  $\tt CTTCCTGATTTCTGCAGCTCTGTGTGAAGGTGCAGTTTTGCCAAGGAGTGCTAAAG$ AACTTAGATGTCAGTGCATAAAGACATACTCCAAACCTTTCCACCCCAAATTTATC AAAGAACTGAGAGTGATTGAGAGTGGACCACACTGCGCCAACACAGAAATTATTGT 15 AAAGCTTTCTGATGGAAGANAGCTCTGTCTGGACCCCAAGGAAAACTGGGTGCANA  ${\tt GTGGTATCCAAGAATCAGTGAAGATGCCAGTGAAACTTCAAGCAAATCTACTTCAA}$  ${\tt CACTTCATGTATTGTGTGGGTCTGTTGTAGGGTTGCCAGATGCAATACAAGATTCC}$ TGGTTAAATTTGAATTTCAGTAAACAATGAATAGTTTTTCATTGTACCATGAAATA 20 TCCAGAACATACTTATATGTAAAGTATTATTTATTTGAATCTACAAAAAACAACAA ATAATTTTTAGATATAAGGATTTTCCTGGATATTGCACGGGAGA

Sequence ID 529

Sequence ID - 530 nt: 660
GACAGCAGAGCACACAAGCTTNTAGGACAAGAGCCAGGAAGAACCACCGGAAGGA

- 173 -

Sequence ID 532

5

10

- 35 Sequence ID 534
  GGGAAGGGAGCTATGAGTGTGTGTGTGTGTGTGTGTCACCTCGAGGTTCACCTG
  GCCACAGGTGCACCCTTCCCACACCCTTTACATTCCCCAGAGCCAAGGGAGTTTAA

- 174 -

Sequence ID 560

- - Sequence ID 561
- CTCAGGGTGATCTCTGAACCCAAACTTGCCCCAAAGAAGGTTGCTCTGTCCTCCC
  ACATCCCCATCTCCCTAGGGCCTTGTTGGGGAGAGGCTCCTCCATCTTTCCCA
  AGTCACACCATCGTTTCCTACGTGGTCTGGACAAGAGCAAGAGCACACCTTGTCCC
  CACCTTCTCCAGAGCAGCCAGAACCCACCTCAGGTGCCTTCCCCATCCGGTGCAGT
  TAAGGCACTTCTGCCAGCACCATGGTATGAGCACTAGACTTGGAGTTAAGATTTGA
  GAGCCCCCTCTGTCACTGTGGAAGCTTGAGCATGTTGCTTGATCTCTCTGAACCTT

  30 GTGTTTCTCATCTGTGAAAGGTGATAATGTGGGGCTGCTGTGAGATTTAAAGGACA
  TAATGCACCTACGGTCCAAGCACTGCCTGGAATACAGCANAAGCTCAACAGATACT
  GGACAACCCATCCCCTTAGTAGAGGCACTAACCATGTGACCCAAGGCAAAAGTGCT
  TAAAAAAA
- Sequence ID 562 nt: 580
  ATTGCATGCAAGTTTGCTGAGCTGAAGGAAAAGATTGATCGCCGTTCTGGTAAAAA
  GCTGGAAGATGGCCCTAAATTCTTGAAGTCTGGTGATGCTGCCATTGTTGATATGG

10

15

20

25

30

5

TCTTACGTTTCTCTGCTTTGTAGTTGTGGCTGTACTTAAAGAAATACAGAATTTCA

Sequence ID - 564

671

nt:

TATATTTAAAAATGTTTAAAATGTGACCCACAGACATTGTAAATGGATTNAAAACT

AACATGAAAAAATATTCAACCTAAAAGAATTCTTAACTTCACAAGTGTTTTACTTC

10

Sequence ID 566

25

- 177 -

Sequence ID 568

15 Sequence ID 570

20

Sequence ID - 571

nt: 457

- 35 Sequence ID 572

CGTCTATTTGNGTTTCTCTCACAATTGGTAAGTTCTCTGTATTGATTGATGGCTA

10

Sequence ID 574

Sequence ID - 575 nt: 209

- 25 CAGGATATCGAGACCATCCCAGACAGCATGGTGAAACTCCGTCTCTACTGGAATAC
  AAAAAGTTAGCCGTGTGTGGGGCACGCGCCTCTAATCCCAGCTATTCGGGAGGCT
  TAGGCAGAGAATTACTTGAACCCGGGAGGCGAAGGTTGCAGTGAGCTGAGATCGC
  ACCATTGCACTCCACCCTGG-CGACAGAGCAAGACTCCGTCT
- Sequence ID 576 nt: 541

  CAGCCAACCCAGAAGGAGCCAGTCTACAACTATGCCTGATCCTCCTCATGGCAGGC
  CACGAAGCATTGCTGCCATGTGTTGAATTATAAAACCCACATTGCTTTTTGAACCC
  TGTTGCGGGTAAAAATAACCAAATTATCAGTCCTTGGAAACCCAGGCAATCAAGTG
  AGTACAAGGTAAAGATAAGTATGGTTTAGAGGAGAAATTATGTTCCTGAACTGGTG

  TCCTTTGATGGCAGCGTCAGCCTTGCTAAGTCAGAGTAGAGGGAGCAGTGACCTTA
  ATAAGCTTTGGTGAGCATCATGTGCACGCGTGGGTGGGAGTCCCTTTCACTGATGC
  TTTTAAAAGTGCTTTTGCAGACCCTGGAAGGGATCCTCCACACATATGAGGTGTGG

GACAGGTAGGCCAGAGAGGATTAGCCCTGCTTTCGAGACTAGAAATCTACAGTCCT GAAGGAGCAGTAATTAATTGGTACACCTGTCAGGGCCAGCCCCCAGGTCTCCTGGC TTTTTCCAGGTTTTCTGTCTCACATGATTTTGCTTTT

5 Sequence ID 577 AAGCACCCGCTCTGTGCATAGCACTATTCTAGGTGCAATAAAAGGGAATCTTAACC  ${\tt TTAGAAATATGAGTTCACTTTCTGGAATTGTATTATCTCCTTTTTCCAGAGAGTAAA}$ AATAAATAAAATCACCATTGTTTACTACAGATCTGCCCCAAACCACATCTGGTTCA 10 CAGAAAGGCTAATTTCTGCCAAATTAAAGATGTAATGAACTCAGTTCCTGCTTTCC  ${\tt TTCTTTAAATTTTCTTCCTCTAATATTGCCTTTTCTTGTACAAGGCAGACCAGGTA}$ 15 TCTTTTTATGCTGTTTTTCCTTTACTAAGAAAAGTATTGCATCTTGAAGACAAACC ATTTCCCAGAGTAGTGATAAAAAATAACACTAAAAAAACTTTAAAGGTGAGTCACT TCATCACCTTGATGAAGTAAAAA

## Sequence ID 578

Sequence ID - 579 nt: 502

CGAATAGCCAAGTGGTCTGACAAGATCGAGAGTAATGAGGCCCATACTTTAGTACA

35 GTCTTGAATGGCCAGATGGTGCTGGGCATACCCCAACCAGAGATATGTAAGTCTTT

ATGTTGTCAAAATTTCCCAGAAACATGAATTTCCCACTAAGATTCATTAAGGAAAA

CTAGAATGAAAACAAAAACGTTCCTTGTATAATATTCATTANAAAGAAATGAAGAA

- 180 -

GGCCGGGCATGGTGGCTCACGCCTGTAATCCCAGCACTTTGAGAGGCCAAGGTAGG CAGATCATGAGGTCAGGAGTTTGAGACCAGCCTGGCCAACATAGTGAAATCCCGTC TCTACCAAAAATACAAAAAAATTAGCCGGGCATGGTGGCACACACCTGTCATCCCA GCTACTCAGGAGGCTGAGGCAGGAGAATTGCTTGAACCTGGGAGGTGGAGGTTGCA GTGAGCTGAGATTGCACCACTGTACTACAGCCTAGGTGACAGTGCAAGACTCTG

Sequence ID 581

CTTCATGAGTGCCCGGTTGCCCAAGTCAAAAACCTGGGAGTGATATAAACTCCCCA
CACATCCAGTCAGTCACTCATCAACTCTATTGATTCTG-CTGCTAAATATATCTCA
ATTGTATTAACTTAAACATATGCATAATACATCTTCTTCTTCACTGCATTTTTGTG
GGCTGCACTTACCTTTCAGGTAACAACAACACTGGCCCCTCTTGCCCTTCTAGTCA

GAAGTGCCAAAATGATGAGAGCTAGCCATGACAAACCCACAGCCAACATTACACTG
AATGTGCAAAACTGGAAGGGCATCCAAACAGAGGAGG

Sequence ID 582

5

10

## Sequence ID 585

## Sequence ID 586

GTAAACTGTTCTCCCGAGGGAAAAAATGGAAGTTATCCTCACAGTTCACTGCCGT

GGTATTTCTTCTGTCCCATGCTTTGCATGACTGCCATGGTACAGCCTTGTTTCAAA

CTGTTCACTGTGATCTGTGGGTCTTTGAGTTTCAGTGAGTTTGCTGAAATGTCGAA

GAAGTAGTTCCAAACTTCAATGTTCAATGAAATTTTTGTTCAAGTTTGAAATGGAG

AGAGCAGCTTTAAAAAGGTACTAAGCCTTTTACAAATTGGTGAGTACTGGCACATGA

GAT

35

Sequence ID 587
TTTTTTTTTTTTCCTTAAAAGGTAACCCCTAAACACAGCTAAAACTATGCCATCAGC

ويرمو ويعرموها ويمرمون ورموها الرابي والعروا مراج مرجوب فالمراج والأراف فالمراج والمراجع والمراجع والمراجع

Sequence ID 588

20 -

25

30

5

10

15

Sequence ID 590

WO 2004/046382 PCT/GB2003/005102

- 183 -

Sequence ID 591

Sequence ID 592

TACTCAATGAAAAACCATGATAATTCTTTGTATATAAAATAAACATTTGAAAAAAA

15 AAAAAA

Sequence ID - 593 nt: 565 CAGGATCAAGGTGAAAAGGAGAACCCCATGCGGGAACTTCGCATCCGCAAACTCTG TCTCAACATCTGTGTTGGGGAGAGTGGAGACAGACTGACGCGAGCAGCCAAGGTGT 20 . TGGAGCAGCTCACAGGGCAGACCCCTGTGTTTTCCAAAGCTAGATACACTGTCAGA TCCTTTGGCATCCGGAGAAATGAAAAGATTGCTGTCCACTGCACAGTTCGAGGGGC CAAGGCAGAAATCTTGGAGAAGGGTCTAAAGGTGCGGGAGTATGAGTTAAGAA AAAACAACTTCTCAGATACTGGAAACTTTGGTTTTGGGATCCAGGAACACATCGAT  $\tt CTGGGTATCAAATATGACCCAAGCATTGGTATCTACGGCCTGGACTTCTATGTGGT$ 25 GCTGGGTAGGCCAGGTTTCAGCATCGCAGACAAGAAGCGCAGGACAGGCTGCATTG GGGCCAAACACAGAATCAGCAAAGAGGAGGCCATGCGCTGGTTCCAGCAGAAGTAT GATGGGATCATCCTGGCAAATAAATTCCCGTTTCTATCCAAAAGAGCAATAA AAAGT

30 Sequence ID 594

35

10

20

#### - 184 -

AAGTTTCCCAAAAAGAAAAGCACTGGCCAAGATGACTTCACTGGTGAATTCTATCA
AGTGTCAAAGATGAATTACTGACATTCATTCACACTCCTTTAAGAAATAGAAGAGG
GGACATCACTTTTCAAAGCATCGACATTCTAATCATTAGTCCCTTGGTTTCCTGCT
CCCAAAGCCAGGTGATGTATCACAAAAAAAACCCCTACAGACCCACTGGGCACAATG
GCTTTATGCCTAT

Sequence ID 599

GACAAAAGAACCATTTGGATACATAGGTATGGTCTGAGCTATGATATCAATTGGCT
TCCTAGGGTTTATCGTGTGAGCACCACCATATATTTACAGTAGGAATAGACGTAGAC
ACACGAGCATATTTCACCTCCGCTACCATAATCATCGCTATCCCCCACCGGCGTCAA
AGTATTTAGCTGACTCGCCACACTCCACGGAAGCAATATGAAATGATCTGCTGCAG

TGCTCTGAGCCCTAGGATTCATCTTTCTTTTCACCGTAGGTGGCCTGACTGGCATT
GTATTAGCAAACTCATCACTAGACATCGTACTACACGACACGTACTACGTTGTAGC
TCACTTCCACTATGTCCTATCAATAGGAGCTTGTATTTGCCATCATAGGAGGCTTCA

- 185 -

TTCACTGATTTCCCCTATTCTCAGGCTACACCCTAGACCAAACCTACGCCAAAATC
CATTTCACTATCATCATCGGCGTAAATCTAACTTTCTTCCCACAACACTTTCT
CGGCCTGTCCGGAATGCCCCGACGTTACTCGGACTACCCCGATGCATACACCACAT
GAAACATCCTATCATCTGGAG

5

10

15

Sequence ID - 600 nt: 595

TTCAAATTCTTGNTAANAGTCTTTGTTCTGAATTTTACTTTGTCTGTTATTCCTAT
AGCCTTTCCAATTTTCTTTCGCTTGGATTTTACGTGATAAGTTTTTTCCCCCATTT
TACTTTTANCAACTCTATATTTTTTAGTTGAGGTTGGGTTTCTTGTAAACAGCATA
TAATTTGGGTTTTTTAATCCAATCTGAAAATTAATGTCCTTAATTTTGTGTTTATA
CCATTTACACATAATGTACTCATATATAAGGTTTAACTGAAACCTACTATCTTGCT
AGTTGTGCTCTACTTGAATTTTTTTTTAGTATTCTGTTTTAATTGACCAACATTTG
ACTGTATCTCTTTGTGTAATTCTTTTTACAGGTTGCTGTAGGCATGACAATATATAC
ACTTAACTTTTCTCAGTACACTGAGAGTTGAAATTGTAGTACTTCGAGGAAAACAT
AGAAAACTTGCAATGATATCGGTTACATTTTACCACCTCCATATGTTGCAATTATT
AAATGTATTAGATCTGCCTACCTCGAAAACCCATCAGTCTTTTAACTTTGCTCTCA
ATGGTGATTCATATTTTTAAAAAAAACTTGAGGCAA

Sequence ID - 601

Sequence ID 602

nt:

522

30

35 .

CAGAAATCGCAATTGAAGACCAGATTTGTCAAGGTTTGAAACTGACATTTGATACT ACCTTCTCACCAAACACAGGAAAGAAAAGTGGTAAAATCAAGTCTTCTTACAAGAG GGAGTGTATAAACCTTGGTTGTGATGTTGACTTTGATTTTGCTGGACCTGCAATCC ATGGTTCAGCTGTCTTTGGTTATGAGGGCTGGCTTGCTGGCTACCAGATGACCTTT

GACAGTGCCAAATCAAAGCTGACAAGGAATAACTTTGCAGTGGGCTACAGGACTGG GGACTTCCAGCTACACACTAATGTCAATGATGGGACAGAATTTGGAGGATCAATTT

20 .

Sequence ID - 603 nt: 624 GACACACGAGCATATTTCACCTCCGCTACCATAATCATCGCTATCCCCACCGGCGT CAAAGTATTTAGCTGACTCGCCACACTCCACGGAAGCAATATGAAATGATCTGCTG CAGTGCTCTGAGCCCTAGGATTCATCTTTCTTTTCACCGTAGGTGGCCTGACTGGC 10  $\hbox{\tt ATTGTATTAGCAAACTCATCACTAGACATCGTACTACACGACACGTACTACGTTGT}$ AGCCCACTTCCACTATGTCCTATCAATAGGAGCTGTATTTGCCATCATAGGAGGCT TCATTCACTGATTTCCCCTATTCTCAGGCTACACCCTAGACCAAACCTACGCCAAA ATCCATTTCACTATCATCATCGGCGTAAATCTAACTTTCTTCCCACAACACTT TCTCGGCCTATCCGGAATGCCCCGACGTTACTCGGACTACCCCGATGCATACACCA 15 CATGAAACATCCTATCATCTGTAGGCTCATTCATTTCTCTAACAGCAGTAATATTA ATAATTTTCATGATTTGAGAAGCCTTCGCTTCGAAGCGAAAAGTCCTAATAGTAGA AGAACCCTCCATAAACCTGGAGTGACTATATGGATGCCCCCCACCCTACCACACAT **TCGAAGAA** 

Sequence ID - 605 nt: 338

ACCTGAGGCCTCGGTGGGGCCAGTGCGACGCTGGCTTAAGGAGCTTGGAGGGGTTCC

TAATACACATTTAATTCAGTTTCTCTTCCCTAAGAGGCTGCCGGAGTTGGGGCCTC

CTCCAGCAGAGACCCCTCGGACCCCTGCAGGGCCTTGGGGTGAACAGGGCTT

CAGTCAGCGCAAGTATTCCATTTGCATTTGGTAATTTTTCATGCCACCTATTTATG

AATATATAAATCTTTATACCAAATCTATTTTTTAAAACATGGAAAAGTTGCCTTTA

TGGAAACTTGGCAGAGCCAGAGTGTACACATTCCTAAACCATTAAACAGATTTCTA

TA

Sequence ID - 606 nt: 556

GGATAATGATACCTCTGACCTTTCTTCCTTTTGGGAAGTACTTGAGTGTGCAGCTG

CATGAGGCCTCAGCAGGAGAGAGATTTTAGGTCCAAGAAGCTATACCAGTAGGACA

AGGCAGGAAAATACTACACTTTCAGGATCAAGCCCCTCTGACTCTCATTTGGAAAC

TGGATGTTTGCTAAGCACCTGCTTCTTAAGGATGCCGAGGGATTTAATGATACTCC

CAGAAACCTGGAGAGATTAATGGGGCCTATGGAGAAGTGCTCTGAACTCAGTGTTG

GGACTTGAATAAAATTAACCATTGTCATGTTTTCAGAACAACTAAGCTGTTTTATA

TTTCATGTGCATGAAAGCCCTAGAACTAAGTTGTTTTTCCAGAAATGAAATAG

ATCCCACAGTTAGATGATGTGGCCATTAGGAAGTACCAAATTTATAAAAATCACTG GAGGTCTGTCTGAGCAGTACCTAATAAAATATAGTATACTGAAAGTGAACAGATCT TTGTCTCTTTTGGCTGCTTGATACTTTATCTGTGTCTGCCGGACAGTGC

Sequence ID 609

## Sequence ID 610

35

Sequence ID 611 TGCAGGATCCGTCGACT

10

- 188 -

Sequence ID - 613

TAAGTNCACAAAGCAG

nt: 341

CCTTATTTTACAGGTGAAAAACCACGAATCAGATAGATTTTTATTTGCCCAAGTCA
CATAATATTAAGAACAGGCCAAGTGTGGTGGCTCATGTCTGTAATCTGAGCACTTT
GGGAGGCTAAGGCGGGTGGATTTCCTGAGCCTAGGAGTTTGAGATCAGCCTGGGCA
ACATGGCGAAACCTCATCTCTACAAAACATACAAAAATTAGTCAGTGTGGTGGTGA
GAGCCTGTAGTCCTGGCTACTCGTGAGGCTGAGGTGGGAGCATCACCTGAGCCTGG

20 GAAGTCGAGGCTGCAGTGGCAACAGAATGGGTAACCTGGACATCAGAGTGAGACCC
TGTCT

Sequence ID 614

Sequence ID - 615

nt: 379

TAAATTTAAAACATTTTAATTAGCTGGCATGATGGCATGCACCTGTAGTCCTACCT ACTTGGGAGGCCAAGGCAGGAAGATTGCTTGAGCCCAGGAGTTTGAGCTTACTGTG AGCTGTGATCACACCACCTGCACCTCCAGCCTGGGTGACAAAGGAAGACCGTATTTCT

AAAAAATAAAAATACAAATACAACTACAAACTAGCACTAGACCAACAGTGACTAT GTACCATGAACTGAGGAATATTATTAATTCCACCATTTGCATCTGAGGTTAACAAT ATGTCAATGACTTAAATAACATCATATCTCTGAGAGTAATTTCTCCTATATTTCCA TGACAAATGTTAGATAATTTTCCATTTTTTCCATTCAACAAAA

5

Sequence ID 617 CATACCCGAGACGATTGTATGAAGAAAATATGGAGGAACTGTTACATGTTCGGTAC  ${\tt TAAGTCATTTCA'GGGGGATTGAAAGACTATTGCTGGATTTCATGATGCTGACTGGC}$ GTTAGCTGATTAACCCATGTAAATAGGCACTTAAATAGAAGCAGGAAAAGGGAGACA  ${\tt AAGACTGGCTTCTGGACTTCCTCCTGATCCCCACTCTTACTCATCACCTGCAGTG}$ 

15

25

10

Sequence ID - 618 nt: 598 GATTAACTTTCATTTTAAGCTCTTCTCTACTAATTCTGTTCGTATGTTTATTCATT TTGCGTTGATCATATTTTGTACACCAGGCACTCTTCTCAGTTTTATATGTGTGTTTA ATTTACTCCTTTCAAGAGCCCTATGATACATGAATTTATCTCCATTTTATAGATGA 20 . GGAAATTAAGACCTAGAGTTACTGAACTTGCCCAAGGTTATACAGCTGATGGGTAG GGCCAGAACTTTGCCTCAGAGAATCTGAATTTCCAAAAAATAACCTAAAAGAGAAA TTTAAGTACTAATTAGTAAGCAAAGAAATGCACATTTAAGGAAGACAGTGCACATT TAAGGAAGACAGTAACCTTTTATCTATTAGAGAAAAACACACATTCTGTCTTTAAC TTGTCTGCTTTGTGGTACACATAAATGCTGGGGATAAACACTTAATAAAATATACT TCCTTCTCTTGAATATCTTGCACTTTAAGTGGGAAGGTAAGTCAACAGAGTAGAGG TGATATATCCAAGTGATAGACTGTTTCATTGCCAGTAG

#### Sequence ID 619

CTGGTCACATTGAAATTGGTGGCTTCATT

30 ATCAGAGAGGGCTACCTTGTGAAGAAGGGGAGCGTGTTCAATACGTGGAAACCCAT GTGGGTTGTATTGTTAGAAGATGGAATTGAATTCTATAAGAAGAAAAGTGACAACA GCCCCAAAGGAATGATCCCGCTGAAAGGGAGCACTCTGACTAGCCCTTGTCAAGAC TTTGGCAAAAGGATGTTTGTGTTTAAGATCACTATGACCAAACAGCAGGACCACTT 35 CTTCCAGGCAGCCTTCCTGGAGGAGAGAGATGCCTGGGTTCGGGATATCAATAAGG CCATTAAATGCATTGAAGGAGGCCAGAAATTTGCCAGGAAATCTACCAGGAGGTCC ATTCGACTGCCAGAAACCATTGACTTAGGTGCCTTATATTTGTCCATGAAAGACAC

10

- 190 -

# TGAAAAAGGAATAAAAGAACTGAAT

Sequence ID 621

Sequence ID 622

25

Sequence ID 624 TGCAGGATCCGTCGACT

# Sequence ID 625

10

25

30

35

- 191 -

Sequence ID 626

Sequence ID 627

Sequence ID 629

CTGAGAGTCACTGTGTTTTTAGCCAAATCTAAGGGAGAAAATGAATATTGATAGCA GCATGCTGTAGCCAGCTCCTTAAAGGAAGGATGGTGCCTGGTACAGAGTTAGAGTT AGTGCTTCAGTAAATAATGAATGTGTGCTAGGTAGGTTCTGCTGGGTAGGCTGCAT GCATTGACCAATTTATTCCTCCTTGTTTCAAAACAGGATTTAAGGGCACTTATATA TATATATTTTTTAGTTTTTAATGTAAATGAGAGAATAAAGATATATATATATGT

#### Sequence ID 630

- - Sequence ID 631
- TNCACTCACACACTCCCAAACCTTAACAAACACATACATGTGCAGCCAACCCAATG

  GGCCAGCCTCTTTTATGCTCCTCACATGTTTCCTTTAACTGGAATACCCATGACAG

  CTCCCTACATAGTTACTTGTAAACTCCTCCTCTGTATAAGTTTTCCTGAATTTT

  TTTGATAAAATTAAGTTGTGCCACCCCTTTATGCTCTCTTANAACTTTGTTCTGTT

  CTCATGGCTGTTCTGCAACGAATCTCATTGTGTTCTCCTACTCAATTACATTCCTG

  CGTCTCCCACTAGATGGCAGACTCTTTGAGAGTAGGAGATTCCCTTGTTATCTCTG

  GATCCCTGGCACTTGCAGAAAGCCTGTTACGTAATAATTGCTCAACAATTAGTTTT

  TAAATAAATGAATTATTTTTAAAACGCCAAAATTACAATGATTGTGCATTAAGTGA

  AAGATGACCATCTAAAAACATAAAGCCATGCTTCATGACATTGGC

#### Sequence ID 632

GACCATTCAGGGAAATTTTATAAAAAATGCAGATACTGTCTTGAGCAGATCGAAAT
GCCGATGAGGTGGATGCAATTTCCTTTTGTGCAAGCAGTGCACGGTGCCCCCCCT
CGGGTGTCCGTGCCTTAGCTTCCCCAGGTGCCGGGACTCACACCTGCTAGG
GGCTGGGCAAGGCCCCGGCTCTGCTTTCTCTGAAGGGCTTGTCCAAGTTCATTGCC
CTGTTACAGGTGGTCAAGACGTCCGGCCGCCTTGACCCAGGCTACCCTTAGCCAAT
ATCCTCTGCCCCTGGGTGGTTGGTGGCTGGGCCTCAGGGTGGCAACGTTAGGGGT
TTGGCGAAAGCCCCCCTGGGATTGAGGGACGGGCTGCACTCCAACCGTCTGC
ACCTGCTCTTCCCCCACCCCTGTGGGACCTCATCTTCACGTGCCATGTGTGCTGAA

GGCCCAGGGCCCAGCAGGGGCAGTGGCACCTGTTGACGGAAAAGCCGAGGTGCTT ACCAATGGACCTTCTGGCCCGCCCTCCCCTGTACTTGTCGGGCATTCAGGGCCCCG ACCTGTGCCTACCCGCA

- 30 Sequence ID 635 nt: 592

  TGAGCGTTGGGCTGTAGGTCGCTGTGTGTGTGTGTCCCCAGAGCCATGCCCGAGA

  TAGTGGATACCTGTTCGTTGGCCTCTCCGGCTTCCGTCTGCCGGACCAAGCACCTG

  CACCTGCGCTGCAGCGTCGACTTTACTCGCCGGACGCTGACCGGGACTGCTCTT

  CACGGTCCAGTCTCAGGAGGACAATCTGCGCAGCCTGGTTTTGGATACAAAGGACC

  35 TTACAATAGAAAAAGTAGTGATCAATGGACAAGAAGTCAAATATGCTCTTGGAGAA

  AGACAAAGTTACAAGGGATCGCCAATGGAAATCTCTCTTCCTATCGCTTTGAGCAA

  AAATCAAGAAATTGTTATAGAAATTTCTTTTGAGACCTCTCCAAAATCTTCTGCTC

- 194 -

TCCAGTGGCTCACTCCTGAACAGACTTCTGGGAAGGAACACCCATATCTCTTTAGT CAGTGCCAGGCCATCCACTGCAGAGCAATCCTTCCTTGTCAGGACACTCCTTCTGN GAAATTAACCTATACTGCAGAGGTGTCTGTCCCTAAAGAACTGGTGGCACTTATGA GTGCTATTCGTGATGGAGAAACACCTGACCCA

5

10

15

Sequence ID - 637

nt: 482

5 Sequence ID - 639 nt: 624 GACACACGAGCATATTTCACCTCCGCTACCATAATCATCGCTATCCCCACCGGCGT CAAAGTATTTAGCTGACTCGCCACACTCCACGGAAGCAATATGAAATGATCTGCTG CAGTGCTCTGAGCCCTAGGATTCATCTTTCTTTTCACCGTAGGTGGCCTGACTGGC ATTGTATTAGCAAACTCATCACTAGACATCGTACTACACGACACGTACTACGTTGT AGCCCACTTCCACTATGTCCTATCAATAGGAGCTGTATTTGCCATCATAGGAGGCT 10 TCATTCACTGATTTCCCCTATTCTCAGGCTACACCCTAGACCAAACCTACGCCAAA  ${\tt ATCCATTTCATCATATTCATCGGCGTAAATCTAACTTTCTTCCCACAACACTT}$ TCTCGGCCTATCCGGAATGCCCCGACGTTACTCGGACTACCCCGATGCATACACCA CATGAAACATCCTATCATCTGTAGGCTCATTCATTTCTCTAACAGCAGTAATATTA ATAATTTTCATGATTTGAGAAGCCTTCGCTTCGAAGCGAAAAGTCCTAATAGTAGA 15 AGAACCCTCCATAAACCTGGAGTGACTATATGGATGCCCCCCACCCTACCACACAT TCGAAGAA

#### Sequence ID 641

CAAGATGACAAAGAAAAGAAGGAACAATGGTCGTGCCAAAAAGGGCCGCGGCCACG
TGCAGCCTATTCGCTGCACTAACTGTGCCCGATGCGTGCCCAAGGACAAGGCCATT
AAGAAATTCGTCATTCGAAACATAGTGGAGGCCGCAGCAGTCAGGGACATTTCTGA
AGCGAGCGTCTTCGATGCCTATGTGCTTCCCAAGCTGTATGTGAAGCTACATTACT
GTGTGAGTTGTGCAATTCACAGCAAAGTAGTCAGGAATCGATCTCGTGAAGCCCGC
AAGGACCGAACACCCCCACCCCGATTTAGACCTGCGGGTGCTGCCCCACGTCCCCC
ACCAAAGCCCATGTAAGGAGCTGAGTTCTTAAAGACTGAAGACAGGCTATTCTCTG

### Sequence ID 642

- 196 -

CACCATGGCCAAATCCAAGAGGTCTTCCTGGAAGAGGGCCCAAACTGGAACCAAAA GAATGCTGTCAGCAGTTGGAATAGAGCTGTGAATT

Sequence ID 643

5

10

20

25

30

35

15 Sequence ID 644

Sequence ID - 645 nt:

CTACAGCCTGGGCAGCGCGCGCCCCAGCACCAGCCGCAGCCTCTACGCCTCGT
CCCCGGGCGCGCGTTATGCCACGCGCTCTCTGCCGTGCGCCTGCGGAGCAGCGTG
CCCGGGGCGCGTGTATGCCACGCGCTCCTCTGCCGTGCGCCTGCGGAGCAGCGTG
CCCGGGGTGCGGCTCCTGCAGGACTCGGTGGACTTCTCGCTGGCCGACGCATCAA
CACCGAGTTCAAGAACACCCGCACCAACGAGAAAGGTGGAGCTGCAGGAGCTGAATG
ACCGCTTCGCCAACTACATCGACAAGGTGCGCTTCCTGGAGCAGCAGAATAAGATC
CTGCTGGCCGAGCTCGAGCAGCTCAAGGGCCAAGGCAAGTCGCGCCTGGGGGACCT
CTACGAGGAGGAGATGCGGGAGCTGCGCCGGCAGGTGACCAACGACA
AAGCCCGCGTCGAGGTGGAGCGCGAACCTGGCCGAGACATCATGCGCCTCCGG
GAGAAATTGCAGGAGGAGATGCTTCAGAGAGAGAGAGCCGAAAACACCCTGCAATC
TTTCAGACAGGAAATCCAGGAGCTGCAGGTCAGATCAAGACAACACCCTGCAAAC

Sequence ID - 646 nt: 600  ${\tt GAGATGTCTCGCTGGGCCTTAGCTGTGCTCGCGCTACTCTCTTTTCTGGCCT}$ 5 GGAGGCTATCCAGCGTACTCCAAAGATTCAGGTTTACTCACGTCATCCAGCAGAGA  ${\tt GAAGTTGACTTACTGAAGAATTGGAGAGAATTGAAAAAGTGGAGCATTCAGACTT}$ GTCTTTCAGCAAGGACTGGTCTTTCTATCTCTTGTACTACACTGAATTCACCCCCA CTGAAAAAGATGAGTATGCCTGCCGTGTGAACCATGTGACTTTGTCACAGCCCAAG 10 . ATAGTTAAGTGGGATCGAGACATGTAAGCAGCATCATGGAGGTTTGAAGATGCCGC ATTTGGATTGATTCCAAATTCTGCTTGCTTTTTTAATATTGATATGCT TATACACTTACACTTTATGCACAAAATGTAGGGTTATAATAATGTTAACATGGACA TGATCTTCTTTATAATTCTACTTTGAGTGCTGTCTCCATGTTTGATGTATCTGAGC AGGGTGCTCCACAGGTAGCTCTAGGAGGGCTGGCAACTTA 15

# 25 Sequence ID 648 AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

- 198 -

Sequence ID - 651 nt: 251

CTTTGGGAGGCCGAGGCGGGCGGATCACTTGAGGTCAGGGGTTCGAGACCAGTCTG

GCCAACATGGTGAAACCCCAACTCTACTAAAAATACAAAAGTTAGCCAAGTGTGGT

GGCAAGTGCCTGTAATCCCAGCTACTCGGGAGGCTGAGACAGGAGAATCACTTTGA

ACCTGGGAGGCGGAGGTTGCAGTGAGCCAAGATCGTGCCACTTCAGCCTGG

20 GCAACAGAGCAAGATTCCGTCCATCTC

Sequence ID 654

GTTGCTAGTAGCGGCAGGAAGATGTCAGGCTCACTTTCCTCTGATTCCCGAAATGG
GGGGAACCTCTAACCATAAAGGAATGGTAGAACAGTCCATTCCTCGGATCAGAGAA
AAATGCAGACATGGTGTCACCTGGATTTTTTTCTGCCCATGAATGTTGCCAGTCAG
TACCTGTCCTCCTTGTTTCTCTATTTTTGGTTATGAATGTTGGGGTTACCACCTGC
ATTTAGGGGAAAATTGTGTTCTG

10

15

Sequence ID 655

AAAAAAAAAAATTTTT

Sequence ID 656

TAGAGGCCTGAATAGGTAGACAATGGCAGCAGCGTTTTTAATCACAGTCCTATTCA
TGCCCTAATTCGGGAGTGATGATTAAAGGACATTAGAGGGAGCACTTTGACATCTG
ATCCTTTGAACTGACGTCTGTGCAGGCTGCACTCCATAGAGCTCACTTGGCCAAAC
TGATTTCCTTAAATAAAGTGCTGTGATTTCCAATGTAGGAAATATTACATTAGAGC
CTATTGAAATGATTAGGAATTGAGGAGCTTTTCTTTAGGTGGGAATGTGGTGTATG
CTGTATACTCACAAAAGTGAGATCATTAATATTTGCATGTACTACTTTGAATATCAG
GGACCACAGAGAAATAGCATGAGAAACGCCTTCCTGCAGTCATGCACTTAAAATGA
ATATGAACAAAAATGTGGAACTCTGCTGTCATAGCTCTCCG

Sequence ID 657

Sequence ID 658

10

Sequence ID 660

### Sequence ID 661

25 CTCTGGCACACATTAGTTCCTCTTATATTACATTGATATAAGCAAGTCATATGGAT
TTATCTGAGTGTAAGGAGAGCTGGAAAAAATAGTTTCTAGCAGGTCAGCCACCTCC
CAGTGAGGGCTGCATACCATAGAAGGGGAGAATGAATTTTGGGAAAACAGGTAATT
ATCTCTGTCACAGAAGGGGATGAAAAGTATGGTAGTTACNCAAGTTANACATCTGT
ATGGAAAATACCACTTGGTTCTACAAATGNGG

Sequence ID - 663

30

35

nt:

35

Sequence ID - 666 nt: 252
ATAATTCAGAACTTCTTCATATGCTCGAGTCTCCAGAGTCACTCCGTTCTAAGGTT
GATGAAGCTGTAGCTGTACTACAAGCCCACCAAGCTAAAGAGGCTGCCCAGAAAGC
AGTTAACAGTGCCACCGGTGTTCCAACTGTTTAAAATTGATCAGGGACCATGAAAA
GAAACTTGTGCTTCACCGAAGAAAATATCTAAACATCGAAAAACTTAAATATTAT
GGAAAAAAAAACATTGCAAAATATAAAAT

## Sequence ID 669

TTACTTTAACCAGNGAAATTGACCTGCCCGTGAANAGGCGGGCNTGACACAGCAA
GACGAGAAGACCCTATGGAGCTTTAATTTATTAATGCAAACGGTACCTAACAAACC
CACAGGTCCTAAACTACCAAACCTGCATTAAAAATTTCGGTTGGGGCGACCTCGGA
GCAGAACCCAACCTCCGAGCAGTACATGCTAAGACTTCACCAGTCAAAGCGAACTA
CTATACTCAATTGATCCAATAACTTGACCAACGGAACAAGTTACCCTAGGGATAAC

30 AGCGCAATCCTATT

 ${\tt TTGTATTTAAACAAAAATTTAAATTTTGGAATCCTCTAAACATTTTTGTATCTTTA} \\ {\tt ATTGGTTTATTAATTAAATAAATCATATAAAAATT} \\$ 

#### Sequence ID 671

## Sequence ID 672

## Sequence ID 673

 ${\tt GGGTTTTCTTTCGGAAGCGCGCCTTGTGTTGTACCCGGGAATTCGCGGCCGCGTC}$ 25 AAGAAAGCCACNTGNNCCCTNGGNCTAATCTGGCTGAGTAGTCAGTTATAAAAGCC 30 CCACAACCTTGGGTCTNTAATNGGGGGGTTTTTTAAATAAANCNTNTNTAAATCCCC CNNNNNNNCNNNNNNNCCNNNNNNNNNNNNNCCCNNNNAAAAATTTTTNC TCCCCCNCCCTTTTTCTTCCTGCCGGCCCCAATTTAAGCCCNGGCGCTTGGGGCAA 35 GGNNNGGGGAA

Sequence ID 674

ACCTCTAGCATCACCAGTATTAGAGGCACCGCCTGCCCAGTGACACATG-TTTAAC GGCCGCGGTACCCTAACCGTGCAAAGGTAGCATAATCACTTGTTCCTTAATTAGGG ACCTGTNTGAATGGCTCCACNAGGGTTCACTTGTCTCTTACTTTTAACCAGTGAAA TTGACCTGCC

Sequence ID - 675 nt: 591 GTATAGAAAATAATGTCCCCAGNGCATAGAAAAAATGAGTCTCTGGGCCAGTGAAT ACAAAACATCATGTCGAGAATCATTGGAAGATATACAGAGTTCGTATTTCAGCTTT  ${\tt GTTTATCCTGTTAAGAGCCTCTGAGTTTTTAGTTTTAAAAGGATGAAAAGCT}$ 10 TATGCAACATGCTCAGCAGGAGCTTCATCAACGATATATGTCAGATCTAAAGGTAT AGACCAGAATAAAATTAATTATATTCTGGTCTTCAAAGGACACACAGAACAGATAT CAGCAGAATCACTTAATACTTCATAGAACAAAAATCACTCAAAACCTGTTTATAAC CAAAGAATTCATGAAAAAGAAAGCCTTTGCCATTTGTCTTAGAAAGTTATTTTTTA 15 AAAAAAAATCATACTTACTATTAGTATCTATGGAAGTATATGTAACAATTTTTATG TAAAGGTCATCTTTCTGTGATAGTGAAAAAATATGTCTTTACTÅAGTTGAAATGAA TACTTTCTGNCTTTGCTAATGGATAGTTATT

- 204 -

TTAAAGAACGNGGACTCCAACGTCAAAGGGCGAAAAACCGTCTATCAGGGCGATGG CCCACTACGTGAACCATCNCCCTAATCAAGTTTTTTGGGGTCGAGGNGCCGTAAAG CACTAAATCGGAACCCTAAAGGGAGCCCCCGATTTAAAGCTTGACGGGGAAAGCCC GGCGAACGTGGCGAAA

5

10.

Sequence ID 682

CACCTGCAGTCCAAGTACATCGGCACGGGCCACGCCGACACCACCAAGTGGGAGTGGCTGCTGGTGAACCAACACCGCGACTCGTACTGCTCCTACATGGGCCACTTCGACCTTCTCAACTACTTCGCCCATTGCGGAGAATGAGAGCAAAGCGCGAGTCCGCTTCAACTTGATGGAAAAAGATGCTTCAGCCTTGTGGACCGCCAGCCGACAAGCCCGAGGAAAACTGAAACTTTTTCCTTAACNACCGAATGGNGGGGANCTTTTCCAACGNTTTT

Sequence ID 683

TTGGTTTCATACTGNTGGGGNTTGAATGNTCCCTNCAACACTNATGTTGANACTTA
ATCCCTAATGNGGCAATACTGAAAGGTGGGGCCTTTGAGATGTGATTGGATCGTAA
GGCTGTGCCTTCATTCATGGGTTAATGGATTAATGGGTTATCACAGGAATGGGACT
GGTGGCTTTATAAGAAGAGAGAAAAGAGAACTGAGCTTGCATGCCC

Sequence ID - 684

nt: 545

GTGGAAGNGACATCGTCTTTAAACCCTGCGTGGCAATCCCTGACGCACCGCCGTGA
TGCCCANGGAAGACAGGGCGACCTGGAAGTCCAACTACTTCCTTAAGATCATCCAA
CTATTGGATGATTATCCGAAATGTTTCATTGTGGGAGCAGACAATGTGGGCTCCAA
GCAGATGCAGCAGATCCGCATGTCCCTTCNCGGGAAGGCTGTGGTGCTGATGGGCA
AGAACACCATGATGCGCAAGGCCATCCGAGGGCACCTGGAAAACAACCCAGCTCTG
GAGAAACTGCTGCCTCATATCCGGGGGAATGTGGGCTTTGTGTTCACCAAGGAGA
CCTCACTGANATCAGGGACATGTTGCTGGCCAATAAGGTGCCAGCTGCTGCCGTG
CTGGTGCCATTGCCCCATGTGAAGTCACTGTGCCAGCCCAGAACACTGGTCTCGGG
CCCGATAAGACCTCCTTTTTCCAGGCTTTAGGTATCACCACTAAAATCTCCAGGGG
CACCATTGAAATCCTGAGTGATGTGCCACTGATCAAGACTGG

30

35

Sequence ID 685

- 205 -

Sequence ID 686

Sequence ID - 687

nt: 268

20 .

25

30

10

Sequence ID - 688

nt: 569

Sequence ID 689

35 CGCAGGGCTTCTGCTGAGGGGCCAGGCGGAGCTTGAGGAAACCGCAGATAAGTTT
TTTTCTCTTTGAAAGATAGAGATTAATACAACTACTTAAAAAATATAGTCAATAGG
TTACTAAGATATTGCTTAGCGTTAAGTTTTTAACGTAATTTTAATAGCTTAAGATT

## Sequence ID 690

CGAAAAGCAAATATAACTTGCCACTAACCAAGATCACCTCTGCAAAAAGAAATGAA
AACAACTTTTGGÇAGGATTCTGTTTCATCTGACAGAATTCAGAAGCAGGAAAAAAA
GCCTTTTAAAAATACCGAGAACATTAAAAATTCGCATTTGAAGAAATCAGCATTTC
TAACTGAAGTGAGCCAAAAGGAAAATTATGCTGGGGCAAAGTTTAGTGATCCACCT
TCTCCTAGTGTTCTTCCAAAGCCTCCTAGTCACTGGATGGGAAGCACTGTTGAAAA
TTCCAACCAAAACAGGGAGCTGATGGCAGTACACTTAAAAACCGCTCCTCAAAGTTC

# 15 AAACTTAGATTTCAGATTT

## Sequence ID 691

30

35

#### Sequence ID 692

AATTCGNGGCCGCGTCNNCCTANGAGGCACCAGGAAATCCCGCGGGGTGGCCCATG
CAGACCAGGCGCACGTGGCTCATGGGGCANAATTGCCAAGGACAGCTCACGACAGT
GCCACCTTCTCACCATTCCAGCCAAGGAGAGATGTGACGTTGGAACTGCTCTGGCA
CTTCTGTCAAGCCTCCCCCGCCCCAATTGCCTTGAGATCTCTGCTCTTTTGTCAGAG
ATTTGCAAAGACTCACGTTTTTGTTGTTTTTCTCATCATTCCATTGTGATACTAAGA
AACTAAGAAGCTTAATGAAAAGAAATAAAATGCCTATGTTGTTGTTCT

10

20 .

25

30

Sequence ID 693

#### Sequence ID 694

Sequence ID 696

## Sequence ID 697

GAACATTTAAAAATAATGCAAATAAGGCTGGGCGTGGGGGCTCACACCTGTAATCC
CAGCACTTTGGGAGGCCGAGGCAGGCAGATCACGAGGTCAGGAGATTGAGACCATC
CTGGCTAACACAGTGAAACCCTGTCTCTACTTAAAAAAATAAAAAATTAGCCAGGC

GTGGTGGTGGCCCTGTAGTCCCAGCTACTCAGGAGGCTGAGGCAGGAGAATGGT GTGAACCCGGGAGGCGGAGCTTGCANTGAGCTGAGATCGTGCCACTGCACTCCAGC CTGAGCGACAGAGCGAGACTCTGTCT

- 5 Sequence ID 698

  TCATTAGAATCCAAGCTTTGAAAAATTTCTGATTAATGCTCATGTATTTCTTTATCT

  TTGTTTTTCCTTGTGAAGAAAGACTTTCACCACTGTCTGAGTGATGATGCTGTTGA

  TAAGGATGATGTCGATGACTACTATATTGCATCTCTCAGGAACAGCTGATGGGAAG

  GGAGGGGCTGCTGAGTTCCCTTGTTCTAGCTAGCAGCACGCTCCTCANAGAGGGGG

  10 CCGAGTTACAGAÇAGCAGCCGCATTCTCATGCAAAATTAGTTTTAAACTGCTAGTG

  TGGGCATCGGTACCTTTTGCCTGGGTGATACCGAAGAATTGTTGAGGATTTAGTAT

  GCTCCGTAGAGACAGTTCAGCCAGTCATTTCTGCATTGGAGAGACTTCTCATACTT

  TCTTTGAAGACTCATAGAAAGCTGGAT
- 15 Sequence ID 699 ATTAAGGTTTGTNCCCAACAAGAATAGATGTAATTAGAAAAANTGNCTTCCTTAC NGGATTTAGAGAACAACACTAACTCCCACCTAATCTATGACAGANATGTACAANAN AGTACCTGTGAAAAATGTGAAAGNATNTGAAAAATGTAACCTTTGGCAGCCTGAGC ATAGTCAACCAGAAAAACTATCTGAATTAAAATAATTGGTCCATAGGTACTATTTT 20 ATTTGGTCCATAAGGATTATTTTTCAACTTTTTTTTCAAGTGTATTATTATGTCA TTTCCCACGTAGGTTACTGATACCTGAAGACTTTTTNCACCTTTAACCTTNCTCGT TGAGGAGCTTTGTANTCTAATAAAAGAGAAATATAAGTAAATGTTAGATATATGGG NGGATAATGGTAACTATGTGCTTAAAGAGGTATAAAAGAAGGGTAGGGAGCAGATA AGACAAAGGAAGGCTATATTATAANGAAGAATATTCCAAGTAGGGAAGAGAAAAA 25 GATATGTTATCCATATAATATTTTATGTGCAGTAGAGAACATGTTCTATAGAANAG ACAGAAGATG

Sequence ID 700

WO 2004/046382 PCT/GB2003/005102

- 209 -

 $\label{eq:condition} AGGGTGTAGAGACCGGGGCAGGGCTTTCTTCTTCTTCTTCTTGGGTTATAAATATCCAT\\ GTCCTGCCATTTGAAGCTGCAAGTGGCACACATGGATGCTGGACAGGCGCTCGCAC\\ TTTCTGGGCAGGCANGGGGCTCAAAGGCAGGACAGCTGGGCAAAAGCACCTTGCG\\ TGGGCCC\\ \\$ 

5

10

15

#### Sequence ID 702

- GTNNTCCTCTCGGAACGCGCCTTNTGTAGCCAGGTGCTACCAGACCNAATACACGG 20  ${\tt TTGTTCCAGCTTGCGCATTCACCGATGGCGTAGATATCCGGATCGGAAGTCTGGCA}$ GGAATCATTAATGACAATACCCCCACGCGGAGCAACGTCCAGACCACACTGGGTTG CCAGCTTATCGCGCGGACGGATACCGGTAGAGAAGACGATAAAGTCGACTTCCAGT TCGCTGCCGTCGGCAAAACGCATGGTTTTACGCGCTTCAACACCTTCCTGCACAAT 25  $\tt CTCAAGGGTGTTTTGCTGGTGTGAACGCGCACGCCCATACTTTCGATTTTGCGAC$  ${\tt GCAGCTGCTCGCCGCCCATCTGATCAAGCTGTTCTGCCATCAGCATAGGGGCAAAT}$ TCGATAAC  ${\tt GTGGGTTTCAATACCTAAGTTTTTCAGCGCGCCTGCGGCTTCCAGACCTAACAGGC}$ CGCAATTCGAGCTCGGCCGACTTGGCCAATTCGCCCTATAGTGAGTCGTATTACAA  ${\tt TTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGGAAAACCCTGGCGTTACCCAAC}$ 30 TTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAAGAGGC CCGCACCCGATCGCCCTTTCCAACAGTTGCGCACCTGAATGGCGAATGGAAATTGT
- Sequence ID 703

  CTGCGCAGACCAGACTTCGCTCGTACTCGTGCGCCTCGCTTTCCTCCGCA

  ACCATGTCTGACAAACCCGATATGGCTGAGATCGAGAAATTCGATAAGTCGAAACT

AAGCGTTAATATTTTGTTAAAATTCGCGT

Sequence ID 704

Sequence ID - 706 nt: 496

CAACCCTCTCCTCAGCGCTTCTTCTTCTTGGTTTGATCCTGACTGCTGTCATG
GCGTGCCCTCTGGAGAAGGCCCTGGATGTGATGGTGTCCACCCTTCCACAAGTACTC

GGGCAAAGAGGGTGACAAGTTCAAGCTCAACAAGTCAGAACTAAAGGAGCTGCTGA
CCCGGGAGCTGCCCAGCTTCTTGGGGAAAAGGACAGATGAAGCTGCTTTCCAGAAG
CTGATGAGCAACTTGGACAGCAACAGGGACAACGAGGTGGACTTCCAAGAGTACTG

5

15

20

10

Sequence ID - 708 nt: 293

CCAGCTTTTATGGTGTTTAATCTAATACACTTAAGCTGCAGTCCCAAAATTAGGG
GTCCTTCAGTCTTGGAGACTATAAGGGAGCCTCTGCACCCAGGGAAAATGTTACCC
TTTACAGGGGGGAAGGGTAAACCAGTAGGGAATACAGTACAATCCCAACCCTACTG
GGAGGGGCGGAGGGAGGTGTTGCCGTCACTGTATTAAGTCGATGTTGGGAAACGT
TTTAACATCTGGAGCCTTTGTGGGTGAAATATGTCTCCAGTTACAACTCCGCAGT
GGATGTGAAGAAG

### Sequence ID 709

- Sequence ID 710
  TGGATTCCCGTCGTAACTTAAAGGGAAACTTTCACAATGTCCGGAGCCCTTGATGT
  CCTGCAAATGAAGGAGGAGGATGTCCTTAAGTTCCTTGCAGCAGGAACCCACTTAG

10

30

GTGGCACCAATCTTGACTTCCAGATGGAACAGTACATCTATAAAAGGAAAAGTGAT
GGCATCTATATCATAAATCTCAAGAGGACCTGGGAGAAGCTTCTGCTGGCAGCTCG
TGCAATTGTTGCCATTGAAAACCCTGCTGATGTCAGTGTTATATCCTCCAGGAATA
CTGGCCAGAGGGCTGTGCTGAAGTTTGCTGCCACTGGAGCCACTCCAATTGCT
GGCCGCTTCACTCCTGGAACCTTCACTAACCAGATCCAGGCAGCCTTCCGGGAGCC
ACGGCTTCTTGTGGTTACTGACCCCAGGGCTGACCACCAGCCTCTCACGGAGGCAT
CTTATGTTAACCTACCATTGCCCTGTGT

Sequence ID - 711 nt: 498
GTGGTACATATACACAAAGGAAAACTATGTAGCCATTAAAAGAAAAGGAACTCCTA
TCATTTGTAACAACATAAATAAATCTGGAGGAGATTAGGCTAAAGGTGAAATAAGCC
AGGCACAAAAAAGACAACTACCATATGATCTTACTTATACGTGTGTGGGAATCTAAAA
AGGTGGAATTTACAGAAGCAGAGAGTAGAATGGTGATTACCAGAGGCTGGGGAGTG
AGGGCAGGAGGTTGGAGAAATGTTGGTCAAAAGGATACAAAGTTTCAGTTATACAGG
ATGAATAAGTTCAAGAGATCTATTGTACAACGTGGTGGTGATAACAATG

ATGAATAAGTTCAAGAGATCTATTGTACAACGTGGTGGCTATAGTTGATAACAATG
TATTGTGTTCTTGAAAAATGCTGAGAGAGTAGATTTTAAGTGTTCTCACCACAAAA
CATAAGTATGTGAGGTAATGCATGTGTTAATTANCTTAATTTAGACATTTCATAAT
GTATTATACATATTCAAAACCACGTTGTACATGAGAAAGATACACAATT

Sequence ID 714

CTGTAACAGAGATTCCTTTTTTCAATAATCTTAATTCAAAAGCATTATTAGACTTG
AAAGGGTTTGATAATCTCCCAGTCCTTAGTAAAGATTGAGAGAGGCTGGAGCAGTT
TTCAGTTTTAAATGAGTCTGCAGTTAATATCAAATGTGAGTTTGGGACTGCCTGGC
AACATTTATATTTCTTATTCAGAACCCTTGATGAGACTATTTTTAAACATACTAGT
CTGCTGATAGAAAGCACTATACATCCTATTGTTTCTTTCCAAAAATCAGCCTT

5

10

15 ATGGCTGGGGAGGCCT

Sequence ID 718

30 Sequence ID 719

35

CGNGGCCGCGTNAACTTTTGATCGTCAGCTGGGGCTGGCAGGCACCTAAATGGGAA GGGTGATAGCAGTGTGTTGGGGGGAGTTTAGGGAACGGTCCTCTACCGATAGAGGC AGCANCTCATTGGAATTTCCTCCTGAAGTTGTCTTGCCCCTTGAATCCTGCAGGAA GGCTGGCAAATGGCCATTTCCCTTCCACTTGAATAGAGACCCATAACTCAAGTATC TGCCCTTAAGACACCACAGGACTGTTCTTCGCGGGCCCTGCCCCTGGATTTGGGAG AGGCAGTCCANCTCACCCAACTAGGCTCTGCANGGGGACCANGAGGGATGGGTTGT GTCCACAGGACCAGCCAGACTGATGAGGGGATGCGCAAGCATATTCTCACCACCTT  ${\tt CTTTCACGTTTACAACANACCAGCNTTCCCTGTGTGGCAGGGGTTACATTGGTCACCGGGGACCTANAATCATGGAGTGCTCTGGGGGATCCGGGCTTGGA}$ 

## Sequence ID 720

TCAGTGTTGAATTTTGTCAGACACTTTCTCTGCATCAATTGGTATGACCATGTGAT
TTTTTTTCTGTAGCCTGTTAATATGGTTAATTTTCAAATATTGAGCTGATTAATTT
TCAAATATTGAGCTCTCCTTGCATCTCTGGAATAAGTACCACTTGGTCGTGGTATA
TATTTCTTTTAATATATTGCTGAATTCTGTTTGATCATGTTTTCTTAAAGACTTTC
GTGTCTGTTTTCATGATAGATACTGGTCTATAGTTTTGTTGTAATATCTTGGTTTG
ATTTTGATATCAGGATAATGCTACCTTAATAGAATGAATTGGAGCCAAGTATGGTG
GCAAATGCCTATAGTCCTAGCTACTCAGGAGGCTGAGGTGGGGGACTGCTTGAC
CCANGAGTTCAAATCTAGCTTGGGCAATGTAGCAAGAC

## Sequence ID 721

## Sequence ID 722

Sequence ID 724

CTCTCTACTAAAAATACAAAAATTAGCTGGGCACGGNGGTGCATGCCTGTAAACCC

AGCTACCAGGTACTCGGGAGGCTGAGGCAGAGAATCGCTTGAACCAGGGAGTCGG

Sequence ID 727

### Sequence ID 728

- 216 -

Sequence ID - 736 nt: 641 GGAATTCCAAGTGCTTGGGGATAATGATACCTCTGACCTTTCTTCCTTTTGGGAAG TACTTGAGTGTGCAGCATGAGGCCTCAGCAGGAGAGAGATTTTAGGTCCAAGA AGCTATACCAGTAGGACAAGGCAGGAAAATACTACACTTTCAGGATCAAGCCCCTC  ${\tt TGACTCTCATTTGGAAACTGGATGTTTGCTAAGCACCTGCTTCTTAAGGATGCCGA}$ 5 GGGATTTAATGATACTCCCAGAAACCTGGAGAGATTAATGGGGCCTATGGAGAAGT GCTCTGAACTCAGTGTTGGGACTTGAATAAAATTAACCATTGTCATGTTTTCAGAA CAACTAAGCTGTTTTATATTTCATGTGCATGAAAGCCCTAGAACTAAGTTGTGTTA TTTCCAGAAATGAAATAGATCCCACAGTTAGATGATGTGGCCATTAGGAAGTACCA AATTTATAAAAATCACTGGAGGTCTGTCTGAGCAGTACCTAATAAAATATAGTATA 10  $\tt CTGAAAGTGAACAGATACTTTGTCTTTTTTTTTGGCTGCTTGATCTTTATCTGTGT$  $\tt CTGCCGTACAGTGCACCCTTAAAGTATTCTACACCAGTGCTTCTCAAACTGGAAAT$ GTGCATGTAAGTCACCCANGGGTCT

15 Sequence ID 739 TGCATGCCCATAGTCCCAGCTATTTGGGAGGCTGAGGCAGGAAAATCGCTTGAACC CGGGAGCCAGAGGTTGCAGTGAGCCGAGATCGCACTCCAGCTTGGCGACAGAACAA GACTCTGTCTCAAAAAAAAAAAAAAAAAAAAATCTTGGGATCCTGAACCCCTTACTC GAAGGGCTAAGGTAGCATCTCAGCATGTCTTATTCGAGACTTCGTANAACCAGACC  ${\tt TGCTGTTTGTAGATGTTAATTAATCAAACCTTTCTCTACTCATTCTGGACCAGTTA}$ 20 - ${\tt AGGTTTTCTCCTTCTCGTATGAGTTTTGATTTTCGTCCTTCGTTGGAGATCA}$  ${\tt CACTTTGGTCTGCTAAGTTGGATGCCTCCCACTGTCTTTCCCTAAGTCTAGGG}$ CTTCANACCCCAGTGTGGGGAGAGGGACTTTCGTTTCCTGCCCCTCACCACATCAG ACACAGGCAGGCAAGAATAAGATGGCCAAAAGGCCGATGAACTTCTTGACCTAGCC TGGGACATTACCTGTTACTAGGTGGACTTCACTGCCTGTGAATGGAAGCTGAAGGG 25 CTGTTTTTTTGGTTTTGTATTTGGACAGGCCAGGCTTANAGAGGGAGAGAACTGGGC TACTCTTCAGCAGTGATCTTTAAAATGCC

Sequence ID 747

30

35

CAGAGTGCAAGACGATGACTTGCAAAATGTCGCAGCTGGAACGCAACATAGAGACC
ATCATCAACACCTTCCACCAATACTCTGTGAAGCTGGGGCACCCAGACACCCTGAA
CCAGGGGGAATTCAAAGAGCTGGTGCGAAAAGATCTTGCAAAAATTTTCTCAAGAAGG
AGAATAAGAATGAAAAGGTCATAGAACACATCATGGAGGACCTGGACACAAATGCA
GACAAGCAGCTGAGCTTCGAGGAGTTCATCATGCTGATGGCGAGGCTAACCTGGGC
CTCCCACGAGAAGATGCACGAGGGTGACGAGGCCCTGGCCACCACCATAAGCCAG
GCCTCGGGGGAGGCACCCCCTAAGACCACAGTGGCCAAGATCACAGTGGCCACGGC

CACGGCCACAGTCATGGTGGCCACGGCCACAGCCACTAATCAGGAGGCCAGGCCAC CCTGCCTCTACCCAACCAGGGCCCCGGGGCCTGTTATGTCAAACTGTCTTGGCTGT GGGGCTAGGGGCCGAAATAAAGTCTCTTTCCTC

5 Sequence ID - 757 nt: 583 GAACCCTGCGGAGGGACTTCAATCACATCAATGTAGAACTCAGCCTTCTTGGAAAG AAAAAAAAGGGCTCCGGGTTGACAAATGGTGGGGTAACAGAAAGGAACTGGCTAC CGTTCGGACTATTTGTAGTCATGTACAGAACATGATCAAGGGTGTTACACTGGGCT  ${\tt TCCGTTACAAGATGAGGTCTGTGTATGCTCACTTCCCCATCAACGTTGTTATCCAG}$ GAGAATGGGTCTCTTGTTGAAATCCGAAATTTCTTGGGTGAAAAATACATCCGCAG 10 GGTTCGGATGAGACCAGGTGTTGCTTGTTCAGTATCTCAAGCCCAGAAAGATGAAT TAATCCTTGAAGGAAATGACATTGAGCTTGTTTCAAATTCAGCGGCTTTGATTCAG CAAGCCACAACAGTTAAAAACAAGGATATCAGGAAATTTTTGGATGGTATCTATGT  $\tt CTCTGAAAAAGGAACTGTTCAGCAGGCTGATGAATAAGATCTAAGAGTTACCTGGC$ TACAGAAAGAAGATGCCAGATGACACTTAAGACCTACTTGTGATATTTAAATGATG 15 CAATAAAAGACCTATTGATTTGG

AGTCCTACATATTTTCCCCCCCAACACAAAAAACCCCAGAAAAGAATTATTTTATACT GGATTTTTTTGGTTGTAGCAGGAACCTAAAGGNGCCAATTGTAACATGCATGTTCT TTTTGGCAAA

5 Sequence ID 766 GTCCATCCTGCAGGCCACAAGCTCTGGATGAGGAACTTGAGGCAAGTCACCAGCCC CTGATCATTTCGCCTAAAAGAGCAAGGACTAGAGTTCCTGACCTCCAGGCCAGTCC  $\tt CTGATCCCTGACCTAATGTTATCGCGGAATGATGATATATGTATCTACGGGGGCCT$ GGCTGCATCGAAGAGTAAAGAGGCTGGAGAGGGGCTGGGCCCAGGGCTCCTCAGAG 10 CAGGAACTCCACTATGCATCTCTGCAGAGGCTGCCAGTGCCCAGCAGTGAGGGACC TGACCTCAGGGGCAGAGACAAGAGAGGCACCAAGGGGATCCAAGAGCTGACTATG CCTGCATTGCTGAGAACAAACCCACCTGAGCACCCCAGACACCCTTCCTCAACCCAG GCGGGTGGACAGGGTCCCCCTGTGGTCCAGCCAGTAAAAACCATGGTCCCCCACT TCTGTGTCTCAGTCCTCAGTCATCTCGAGCCTCCGTTCAAAATGATCATCATCA 15  ${\tt AAACTTATGTGGCTTTTGACCTTTGAATAGGGAATTTTTTAAAATTTTTTAAAAA}$ TT

#### Sequence ID 768

#### Sequence ID 773

GAGGAAAGGGGAGTTAATATTTAGTGGACAGAATTTCAGTTTTACAGATGAAAAGA
GTTCTGGAGATAGACGGTGTTGATAGTTGCACAGCAGTGTGAATGTGCTCATTGTT

ACCGAACTTAAAAATGTTTAACATAGTATTATGTGATTTTTATTTTTGCCACTTAAA
AAAAAAGAATGAAGTACTGATACATGCTACAACATGGGTGAGCTTTAAATACATTC
TGCTCAGTGAAATAAGCCAGATGCAAAAGATCACATATTATATAATCCACTTATAC

10

15

Sequence ID 776

TTTTTTTTCATAAGAGGCAAGTACAAGAAAAAGCTTAATTACTTTAACTTCTAAG
TAGTTTGGAATCTAAATAAATAGGAGTTACCAAATATATGCGCTTCTGTGAATAGT
TTTCCCCCACATGYTTATTTATATTTTTTGCATCTATCAAACCTAACAGATTCTAA
AGTCTCTGGTGATAATGACAATATCTGCTACGGAGAGACTAGCCTGGGGGAAGAGG
ATCTCCCTGAACAAGGATAGCGGAGTTGCTGCAGCTTTCAAATGAAGCTGGACATT
TAGCTGCGGGGGTAGCACCCTTTGATCAAGGCAGCCCAAAGATGAGTTTCAGGGAT
GGGACTGACAGAAGAAAAGTTCTTCCCAGCCCTTTCTACTTTTTCTCTTTTGTTT
CTCAGGCTTCTGGCCGTCTTCAGTTTTCACAAGTTTCACCTCAACCCTAAACAGT
ACTTCTGTGAAGTACCCTTTGGCCCCTCGTTTTCAGCTCCTAAACTCACCTGGAAA

Sequence ID 782

Sequence ID - 785 nt: 556

CTTTTCTCTGGGTATAGATTTACCCTAGCACCTATCTCATTATATTGAATTTCCA

30 GCATATTTAAATAAACTATTAATTAGTCACACTATTCTTAAAAGTCACACTATCA
ACTAATCGTGACCGCAATTATCTAGGGGTGATAATCTGCTGAGTCTACTCTTTAAA
TACACTGGGACCCAGCATATTGAGTTATATTGGCACAGAAACTTCACTCTGGGTAT
AGATTTACCCTAGTACCTTGCCGGCAGGATCCTATTATTCATGGTTGTACAAGCAA
GGTTCAGGGAAGAGGCTGGCACAGAGAAGGTACCTGGTAACTGTTGTTTGAGGCTG

35 AATTCAGCTCAACTCAGCTCCAGTAGAGATGGTGTCCCCTTCTCTACCGTGTTGAG
ATAGTGTGCAGTCCCTTCCTAAGGGCTGTTACCCACCGCAATAGGACTTGTCAGCT

# GGNGGNTTTAGCACCAATTTAGTAAACACAAACTGTCTGAAATATTTTGGAT

Sequence ID 796 GAACATTCAAGATAGTGAGAGGAAGAAAAAGATATGGCTGTACGGGACCGAGGTCT CTTCTATTATCGCCTCCTCTTAGTTGGCATTGATGAAGTTAAGCGGATTCTGTGTA 5 GCCCTAAATCTGACCCTACTCTTGGACTTTTGGAGGATCCGGCAGAAAGACCTGTG AATAGCTGGGCCTCAGACTTCAACACACTGGTGCCAGTGTATGGCAAAGCCCACTG GGCAACTATCTCTAAATGCCAGGGGGCAGAGCGTTGTGACCCAGAGCTTCCTAAAA CTTCATCCTTTGCCGCATCAGGACCCTTGATTCCTGAAGAGAACAAGGAGAGGGTA  ${\tt CAAGAACTCCCTGATTCTGGAGCCCTCATGCTAGTCCCCAATCGCCAGCTTACTGC}$ 10  ${\tt TGATTATTTGAGAAAACTTGGCTTAGCCTTAAAGTTGCTCATCAGCAAGTGTTGC}$ CTTGGCGGGGAGAATTCCATCCTGACACCCTCCAGATGGCTCTTCAAGTAGTGAAC ATCCAGACCATCGCAATGAGTAGGGCTGGGTCTCGGCCATGGAAAGCATACCTCAG TGCTCANGATGATACTGGCTGTCTGTTCTTAACAGAACTGCTATTGGAGCCTGGAA ACTCAGAATGCAGATCTTTTGTGAACAAAATGAAGCAAGAACCGGAGACNCTGAAT 15 AGTTTTATTTCTGTATTAAAAACTGNGATTGGAACAATTGAAGA

Sequence ID 801

20

25

30

CCACTCCACCTTACTACCAGACAACCTTAGCCAAACCATTTACCCAAATAAAGTAT
AGGCGATAGAAATTGAAACCTGGCGCAATAGATATAGTACCGCAAGGGAAAGATGA
AAAATTATAACCAAGCATAATATAGCAAGGACTAACCCCTATACCTTCTGCATAAT
GAATTAACTAGAAATGAGGATTCTGACCTTGACTTTGATATCAGCAAATTGGAACA
GCAGAGCAAGGTGCAAAACACAGGACATGGAAAACCAAGAGAAAAAGTCCATAATAG
ACGAGAAATTCTTCCAACTCTCTGAAATGGAGGCTTATTTAGAAAACAGAGAAAAA
GAAGAGGAACGAAAAGATGATAATGATGATGATGAGAGACATAGCAAGATGT
GAACAACAAAGATTTTTTTGATCCAGTTGAAAGTGATGATGAAGACATAGCAAGTGATC
ATGATGATGAGCTGGGTTCAAACAAGATGATGAAATTTACATCTTTAGAAAAAAGAGTTA
TTAGAAAAAAGCCTTGGCAGCCGTCNGGGGGAAGTGACGCACAGAAGAACCAAGA
AATAGCTTCCTGGANGAGACCCTTGCACTTTACCCCATGCTGCTGGATGG
AATAGCTTCCTGGANGAGACCCTTGCACTTTACCCCATGCTGCTGGATGG

Sequence ID - 814

nt:

132

Sequence ID 817

Sequence ID - 821

nt:

370

AAAGAGCTCCCAAATGCTATATCTATTCAGGGGCTCTCAAGAACAATGGAATATCA

TCCTGATTTANAAAATTTGGATGAAGATGGATATACTCAATTACACTTCGACTCTC
AAAGCAATACCAGGATAGCTGTTGTTTCANAGAAAGGATCGTGTGCTGCATCTCCT
CCTTGGCGCCCTCATTGCTGTAATTTTGGGAATCCTATGCTTGGTAATACTGGTGAT
AGCTGTGGTCCTGGGTACCATGGCTGGTTTCAAAGCTGTGGAATTCAAAGGATAAA
TTAATGAAGAAAACAAGCGGAGCTGAAGAAGAAAGTACAATATGGTGCTGTCTTCC

35 TAATGAAATAAATTCACTAAATGGACATTAAAAA

15

20 .

10

5

Sequence ID 833

30

35

25

Sequence ID - 837 nt: 603

TGAGGNTGGTCATGATGCANAAGCTACTCAAATGCAGTCGGCTTGTCCTGGCTCTT

GCCCTCATCCTGGTTCTGGAATCCTCAGTTCAAGGTTATCCTACGCGGAGAGCCAG

GTACCAATGGGTGCGCTGCAATCCAGACAGTAATTCTGCAAACTGCCTTGAAGAAA

AAGGACCAATGTTCGAACTACTTCCAGGTGAATCCAACAAGATCCCCCGTCTGAGG

ACTGACCTTTTTCCAAAGACGAGAATCCAGGACTTGAATCGTATCTTCCCACTTTC

TGAGGACTACTCTGGATCAGGCTTCGGCTCCGGCTCTGGATCAGGATCTG

- 223 -

GGAGTGGCTTCCTAACGGAAATGGAACAGGATTACCAACTAGTAGACGAAAGTGAT
GCTTTCCATGACAACCTTAGGTCTCTTGACAGGAATCTGCCCTCAGACAGCCAGGA
CTTGGGTCAACATGGATTAGAAGAGGATTTTATGTTATAAAAGAGGATTTTCCCAC
CTTGACACCAGGCAATGTAGTTAGCATATTTTATGTACCATGGNTATATGATTAAT
CTTGGGACAAAGAATTTTATAGAAAATTTTTAAACATCTGAAAA

10

5

Sqeuence 849 nt: 622  ${\tt TTTTTTTTTTTTTTTGAGAATGGAGTCTTGCTCTGCCGTCCAGGCTAGAGTTCAG}$ TGGTGCGATCTCAGCTCACCTCACCTCCTAGGTTCCAGAGATTCTTGTGC TTCAGCCTCCTCAGTAGTTGAGAATACAGGAACACGCCACCACCCCTAGCTAATTT  ${\tt TTGTATTTTAGTAGAGATGGGGTTTCACCATGTTGGCCAGGCTGGTCTCAAACTC}$ 15  $\tt CTGGCCTAAGTGACCCACCTGCCTCAGCCTCCCAAAGTGCTGGGATTATAGGCGTG$ AGTCATTGTCCCCAGCCGGATGTTTTCATCTTGATTTTGCCTTAGTTTCTAAATCTC ATCCTCTCCATTTTCTCCTGTTAGTAGTCACAGAGAACCAAATTCTGTCAAGTTAT GAAACTAAAGTCTCTCCACAAGTCTTCCTGTGTTCTGCCTCAAGTGAACTTGA AAGAACATCAGTTTGTGGGAAGGTTGAAGACCGAATGATCTGCTGGGAAATCACTG 20 AGGCATTGCCATTCTCTTGAGGAATTTCATTTTCATCGAAGTTTCGGTTTATATCC NTGAGC

35

Sequence ID 864
TTGTGTTTTTAGGACTCCTTATCTAAATTAAGGCAGAGAAGTTACAGTATTTATAT

10

15

- 224 -

Sequence ID 867

35

AAAATGCATACTAATATTTCAATGTCTTTCTTCAATTTGAAAAGCTCTTGAATATC
TACTTGTGATAGCCCTAAGAGCTGAGATAATTATTTCCAGGAGGTTGAATCCCTGA
TTCTTAACTGTTCAGCAATGCATAAGCAAGAGAGAATATGACATAAGAGGACCATT
TCTACATTAGCCATTTTTTTTCACAAGATACCTATGTGAATACAGGGCACCTGGGA
NGGTAAGTGGAGGACTATTTCTAACTATATTTATAAGCACATACTGATATTGNTGA
ATCAAAACCTACAGCAGTGCTTCTCAGATGGGAAGGGAGACAATGTGTAAGGAGAT
CAGGAATTCATTAGTCACCTTTCAGATGGTTTAATGCATACAGCTGTACCG

Sequence ID 870

- GGAGTTTGAGCAGÁTCCTTCAGGAGCGGAATGAACTCAAAGCCAAAGTGTTCCTGC
  TCAAGGAGGAACTGGCCTACTTCCAGCGGGAGCTGCTCACAGACCACCGGGTCCCC
  GGCCTTCTGCTCGAGGCCATGAAGGTGGCTGTCCGGAAGCAGCGGAAGAAGATCAA
  GGCCAAGATGTTAGGGACACCAGAGGAAGCAGAGAGCAGTGAGGATGAGGCC
  CATGGATCCTGCTCTCCGATGACAAGGGAGACCATCCCCCACCCCCGGAGTCCAAA

  ATACAGAGTTTCTTTGGCCTATGGTATCGGGGTAAAGCTGAATCCTCTGAGGATGA
  GACCAGCAGCCCTGCACCCAGCAAGCTAGGGGAGAAGAGAGGAGGCCCAACCACAGT
  CTCCAGCTCCTGATCCGCCCTGTTCTGCCCTCCACGAACACCTTTGTCTGGGGGCC
  TCAGCCGCCCCAGAGGCCTGACTTAGGGGTCTGGCTGTGGAAGGATGTGTGGCCTC
  AAATGAGGACAGGGCTCCCGCCTTCACAGCCCTCGCCAGGGGTCTGCCCCAATCCT

  GGCCTGCATCAGGGAAGGACGGGTCTCACAG
- Sequence ID 871 nt: 642 GCAAGTCTTCAGTATGTACATTTATCCCCTAGAAGAAGAAAAATTAGTTGTGCATG AAAAAGAAACATTAACTGCAAAGCTAAATGCTCACACTCTAAATCAGTGCTCTCCA 25 TTATTCTTTTTAATGGACACTTCATACATAAATATATTCACAATATATTAATATAT ACATAATGTATAAGCATACATATTGAATGTGCAGTCAAAAAATGTACTAATGGAAT GCTCTACCAAAACAAGTTCACGTTCATCTGTAAAATGGGAATAATATTTTTAAAAG GCATACAGTCTGAACATTTTTAGATTATTCATAAAATCTATTCAGAAAGTTAAACT AAAAAATTTAACGTATGCCTATAACAAATTTTGTACTTAATGTAATTGNTTTTCAT 30  ${\tt CCTGAGATCTAATATCCTCGTTTTTAAGTAGAGCCACTTGTTTGCTACAGTTTAGT}$ CAAAACGTTAACATTAGATGGGTAAAGTAATATGAAATCTTTCTACTACTCCAAAA TAGAAAACAGAACATTAAAAAGATAAAAATTCAAACATACTTACCAGTAGATTTTC AACTGNGCAAAAGCTCATTGCATGGG

Sequence ID 873
GTTTTCCACCGTGAAGAGAACATTTCCTCTGGGAATGACAAAGCCCTCAGGAACNG

10

30

Sequence ID 875

#### Sequence ID 879

20

25

30

5

### Sequence ID 881

TCGACTCTGATTTTTTTTTCTCCTTCCTCGCAGCCGCGCCAGGGAGCTCGCGGNGC
GCGGCCCCTGTCCTCCGGCCCGAGATGAATCCTGCGGCAGAAGCCGAGTTCAACAT
CCTCCTGGCCACCGACTCCTACAAGGTTACTCACTATAAACAATATCCACCCAACA
CAAGCAAAGTTTATTCCTACTTTGAATGCCGTGAAAAGAAGACAGAAAACTCCAAA
TTAAGGAAGGTGAAATATGAGGAAACAGTATTTTATGGGTTGCAGTACATTCTTAA
TAAGTACTTAAAAGGTAAAGTAGTAACCAAAGAGAAAATCCAGGAAGCCAAAGATG
TCTACAAAGAACATTTCCAAGATGATGTCTTTAATGAAAAGGGATGGAACTACATT
CTTGAGAAGTATGATGGGCATCTTCCAATANAAATAAAAGCTGTTCCTGAGGGCTT
TGTCATTCCCAGAGGAAATGTTCTCTTCACGGTGGAAAACACAGATCCAGAGTGTT
ACTGGCTTACAAATTGGATTGAGACTATTCTTGTTCAGTCCTGGTATCCAATCACA
GTGGCCACAAATT

#### Sequence ID 883

TCATTTACATTAATACTCAAAACTGCTCGATTAAGCAGGTGCTGTTCTTATCGCCA
TTTTGCATATGATGAGAAAGGGTAAGGTCACCCAGCTAGTATTTGGCTCACAGCAG
GCCTTAAGACTTGGTTTGTGTGACTCATCAGTCCACGCTCCTAAAACCACTAAGTT

10

15

20

5

Sequence ID 885

Sequence ID 887

Sequence ID 889

CAGAGAGCTTGTTCCCTCCCTGTGCATGCAAACAAGAGGGCATGGGAGCACA
CAGAGAGATGGCAGCCACCTACAAGCCAAGAGGAGAAGCCTCACAATCAAACTCTC
GCTGCTGGCGAGAGTCTTGGACTCTTGTTCTTGGACTTCCAGCCTCCAGACTGTGAGA
AACAAATTTCTGTTGTTTCAGCTTCTCAGTCTCTGGTGTTTTTGTTATTGCAGCCTG
AGAACACAGCTGTACNATTATNAGGGAAACAGAAAACACTGATACTTAACAATGCT
AAATGCAATTATTTATTTGCTTTTCAGTCTCTACAAAACGTTCTAAAACACTAATCT
AAATATTAACAGTAAAAATATTTGCATAACTAATGGAAACTAAGAAATCATATGACC
AATATTTCACTTATTGGTAATCTTACTCTACTGATTTCCCCCCCAGACTGTGATTTT

TGAACTTCCTTGCCTTTCTCCTGTCTTTCTGNGTTTATTCATGGAATTCCAGTTAT
CTGGGCTTGAAATTGCAGGCTCTCCTAACTTAAGCAAAATCTGACAGATCAGCAAA
ATGAGATAAATGTTTCTTTTTCTTGTGACTGCATTAAATCAGATACAACTCAGC
ATTAAAAAGCTATCTTTGNAAAATGNTGGTACTAATAAATTAGTCTTA

5

Sequence ID 890

CCAGTTCCACATTCAGTGAAGTCATGAACTTGAAATTGGCCATGATCAAAAAGTAT

TTAAATCACAGAAGTTGCAAATGCCACAAATCAAGGTCTTTTTCTCTTGGAGAACC

TGTTAAACATTTACCAACTCACGACCGCCATGCACCCAATACTGCAATAGGTCTAT

AGATGCAGATACTGTCTCCATGAATCTTATAGGCTAGAAAGGAAATAGATAAGTAG

TCCTACCAGAAGAACATGATGAAGGCATTTGTGGTAAACAGAATGATGGCCCCCCA

AAGATGTCCACATCCTAATCCCTGAAGCCTATGAATATACTACTTTACTTGGCAAA

AGGGACTTTGCCACAGGTTTTTAATTAAGGACCTTGAAATAGAGAGATTATCCTGG

ATAATCCAGATGGCCCCAGTGTAATCCCAAGGGTCCTCACAAAGGGTAGGAAGAG

15

AGCCAGAGTCAGAGAAGGAACGTAGCAATGGAGGCAGAGGTCANAGAGAGATCTG

CAGATGCTGCTGTTTGGCTTTGAAAATGAGGAATGCAGGTGACCTCAANGNGCTA

GATGATGCAAGGAAACAAATAATCTCCTATGAACCCTAGGATGGGCATTATTATGA

GTCCTATTTTATAAACAAGGAACTGACNTCCAGAAAGATAAATGC

20 Sequence ID - 891 nt: 626 GGCAGAGGTTGCAGTGAACTGAGATCATGCCATTGCAATCCAGCCTGGGCAACANG AGTGAGACTCCATCTCAAAAAAAAAAAAAAAAAAAGACAAGAGTNTCCACTCTAAACA CTTNTATTCAACATAGTCCTGAAAGTCGTAGCCACAGCAATTTAACAAGATAAAGC AATAAAATGTATTCAAATAGAAAAAGAGGAAGTCAAATTATCTTCACTGGNGATAT 25 AATTCTCTACCTGGGAAACTTCACCGAAAAGATTTCACCAAAAGATTTCTAAGCC TAAATAATGACTTCAGCAAAGTCTCACCATACAAAATCAACATACACAAATGAGTA ACAATAGCTACAAACAAAAAAATATGTACCTAGTAATACATTAAATCAAGGNGGTA AAATATCTNTACAACAAGAACTACAAAACTGCTGAAAAAAAAATAGAGACACGCAAA TAAGTAAAAAGGCACTCCATGCTCATGAATTTAAAGAATCAATATAATTAAAATGT 30 CCGNGCTGCCTAAAGCAACTTACAGATTAAAGGCTATTTCTCTCAAACTATAAATG CACCTTTTTA

Sequence ID - 893

nt: 585

GTCATTGCTGGGTGGCGCCAGCCCTCAGACTTGCCTCTTTGCAGTAGGAAGAAGGC CTCCCCACATACCTTCCCACACTCATCACCTTAAGCCAGACTCGGTGTCCAGTGAA TATGACCATCTCTTGCCCATTTTCTAATGAGTGTTTTCATTAATGAGTTATAAGAA

35

TGTGGTGGGTAAATCTATGGGCTTTGAACTAGTGAATCAACTTGGTTTCAGAATCT
GGCACTGCTACTTACTAGTGAATTTAAGCAAGTTATTTCACCTTTCAGAGTGTCAG
TTCCCTCATGCATACAAGGAAGATAAAAAAATAATGTNTACNAAAGTATTGGAGTAA
TTAATACATGGAGAACTACATGTAAAGCGTTTAGCATGATGTCTGACATATTAAGC
ATCCAATATTAGTNGCTTGCAGAATTATTAGTAAAAGAGATTGCTTCTGAAAGCCA
TTCCAATTCTTAAATTTTATAATGCCACATTTGAGGTCACCTGAAGTCGTGTATAA
CATGTGTACATTTTTGCGATTTATTTTTTCAATTCCCANATTAAAGGCATAGAGAT
ATCCTAGCNANGGACTCCAAGTGTG

10 Sequence ID 4 895 nt: 560  ${\tt AAATGGGGCATCTTAGGGTTTAAATATGTCCAGGGTCACTGAGGATCAGATCCTAG}$ GGTTCCTTTGACTCAAGGCTTTTGTCTCAGCAAAACGTCACCTTCCAGCAGGAAGG 15 TTTAAAATAATGCAGGCACCGTGCGCATAATTTAAAAAATCAGTGCTAAAACCCTT  ${\tt TTCTTTTATTATTATTATATATTATAGTTTTAGGGTACATGTGCACAACGTGCAGGT}$  ${\tt TTGTTACATATGTATACATGTGCCATGTNGGTGAGCTGCACCCATTAACTCGTCAT}$ 20

10

15

20

5

Sequence ID 898

Sequence ID 899 TCNTTCGGAACGCGCC

25

30

35

Sequence ID 900

- 232 -

Sequence ID 903

GGAAACATAAGCTTGTTTCAGTACACTCACGCTGTAGATTAATTCTGATATTACAT ATCTCCATCAGACTTTGTACCCTCTCTCTCTCTCCATCCCTTACCCTTACCGATTAGGT TGGTATTACCTAAAAATCCATAGAAAATGTCCAGGTGAATTGCCTTATGCTTTCTA CCCCATAAGGTATAATT

Sequence ID 904

20 .

5

Sequence ID - 905 nt: 655  $\tt CTCAGCTCTTGCCTGGTCACCTTGTGGCTTTTACCATCCTCATCCCCTGTGCCACC$ CACATCCTGCCACTTCTGCATGGAGTTGGGGGGCCATTGGAGAAAAGAGGTTA AACAAGCAGTAATTTACTTGAGTACAGTCTTTGAGCCAATGAAATGCCAGTCATCA 25 TTTCCCAGGGGTACTTGTCATCTTGTCAACAACCCGCTGATAATGCTCCTTCAATG TGAATAGCAAAAGTAGGGAGAGACGCTGAATGAAGAAGATGCCTACCCCTCAGGAA GACTGCTGTCCGCCTCCAGGCCTGCATGCACACACCCATGCCCACCTGCACCCCCA  ${\tt GCACCACGCCCACACTCACTCGCACACACCCCACATGCCAGTGTTTTGGGGTTGGCA}$  ${\tt TCTGTCTCTGTTTAGTTAGTGGGAATTTGGTCAGTTTAGAGGATTTAATAAGTCCG}$ 30 GATGTGTTTTCCCACTACCTTCCAGGCCAGCCGAGCCCACTGGCCANGGCCTGGCC CGGTGACCTCGGTTGACACTGTCCTCANGCCACTCACTT

Sequence ID 906

CAGAATTTCATGTTTATGCTGCACAAGGCCTGTATTTTATAATGGTGGCTCTTTTG

GACGATĠACTTCCTCGATGGTGAAACTTCCAGTAATCTCCCTCATĊATACTGAAAT

فكالم موافع والمنافرة والمواري والمراق والمراق والمراق والمراق والمنافرة وال

5

10

15

## Sequence ID 908

ACCTGACTTCAAACTATACTACGAGGCTACAGTAATCAAAACAGCATGGTACTAGT
ACAAAAACAGACCAATGGAACAGAATAGAGATCTCAGAAATAAAACTGCACATCTA
CAACCATCTGATCTTCAACAAACCTGACAAAACGAGCAATGGGGAAAAGGATTCCCT
ATTTAATAAATGGTGCTGGGAGAACTGGCT-AGCCATGTGCAGAAAATTGAAACTG
GACCCCTTCCTTACACCTTATACAAAAATTAACTCAAGATGGATTAAAGACTTAAA
TGTAGAACCCAAAAACGATAAAAAACCCTAGAAGAAAATCTAGGCAATATCATTAAGG
ACATAGACATGGGCAAAAATTTCATGATGAAAAACTATCAGCAACAAAA
GCAGAAACTGACAAAATGGGCTTCTGCACAGCAAAAGAAACTATCGTCAGAGTGAAC
AGACAACCTACAGAATGGGAGACAGTTTTTGCAATCTATCCATCTGACAAAAGTCT
AATATCCAGAATCTACAAGGAATTTAA

30

35

WO 2004/046382 PCT/GB2003/005102

- 234 -

 ${\tt ATCAATTCTAAAGCATTTGCTTGTTTGAGCAGATTTTCTGTGTCTGAGGTATATAG}$ ATAACTTATCTTTTTATGACTAAATCCAAGTCCTTAGTTCCTGTTGGAATTCAAAA TAAGTATTCTTCCAAATCCCTTTTTACAGATGATGATTCTGATACCGAGACGTCAA ATGACTTGCCAAAATTTGCAGATGGAATCAAGGCCNGAAACAGAAATCAGAACTAC CTGGNTCCCAGTCCTGTNCTTAAAATTCTAACTCGAC

Sequence ID - 911

nt: 595

GAGGGTGTAGAAGAAGAAGAAGGAGGTTCCTGCTGTGCCANAAACCCTTAAGAA 10 AAAAGATGCTTCGAAAGGCAAGGAGGAAGCTTATCTATGAAAAANCAAAGCACTAT CACAAGGAATATAGGCAGATGTACAAANCTGAAATTCGAATGGCGAGGATGGCAAG AAAAGCTGGCAACTTCTATGTACCTGCAGAACCCCAAATTGGCGTTTGTCATCAGAA TCAGAGGTATCAATGGAGTGAGCCCAAAGGTTCGAAAGGTGTTGCAGCTTCTTCGC  ${\tt CTTCGTCAAATCTTCAATGGAACCTTTGTGAAGCTCAACAAGGCTTCGATTAACAT}$ 15 GCTGAGGATTGTAGAGCCATATATTGCATGGGGGTACCCCAATCTGAAGTCAGTAA ATGAACTAATCTACAAGCGTGGTTATGGCAAAATCAATAAGAAGCGAATTGCTTTG ACAGATAACGCTTTGATTGCTCGATCTCTTGGTAAATACNGCATCATCTGCATGGA GGATTTGATTCATGAGATCTATACTGTTGGAAAAC

20

25

30

5

Sequence ID - 912 nt: 651 CATTTCCAGAGTTTATGTGAATTGAATTGAACTATGGTTTATGTTACTGTCAGTA GAATGAAGTACGAATATTTGAAAAATACACCTTCAACTTCAAAGTGATTCTTGACA AAAATTATAAGGAATCATTTTGGACACATTTTCTGGTAGAGCCTTGTAAAAATTAA  ${\tt AACCAAGTGTTTTTCAAGAAGAACTGTAATACATAATCAGGAATTTGAGTAGGG}$  ${\tt AGATTATTTGTTATTTAAAATTAAAGTGGCTGTGTAGTTTTAACTTTAGTATTGC}$ AGGTAGAGTAAGCTTACATGATAACAAAAATCTTGGTCTTAGTGACTTAATGATTC TGATATTTATTGATTGATTGGTTATCATTCCAAATATTTTAAAAGATAATAGCTGG  $\tt CTGGGTGCGTGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCCAGGACGGGCG$ GATCACGAGGTCAGGAGATCAAGACCATCCTGGCTAACACGGTGAAACCCCGTCTC TACTAAAAATCAAAAAATTAGCCGGGTGTAGTGGCGGGCACCTGTAGTCCCAGCTA  ${\tt CTCAGGAGGCTGAGGCAGGAGATGGCATGAACCTGGGAGGCGGAGCTTGCAGTGA}$ GCTGAAATCGTGCCACTGCCTCCACCTGGCGACAA

35 Sequence ID 913  ${\tt GTGAGGTGGGGACTTCATTCATTGTCCTATTTCTATCTCCACTTTGTGCCTGGAGA}$ 

- Sequence ID 914

  GGCGCCTGCTGGAGGAGAGAGCTCTGCTGGCATGAGCCACAGTTTCTTGACTG
  GAGGCCATCAACCCTCTTGGTTGAGGCCTTGTTCTGAGCCCTGACATGTGCTTGGG
  CACTGGTGGGCCTGGGCTTCTGAGGTGGCCTCCTGATCAGGGACCCTCCCC
  GCTTTCCTGGGCCTCCAGTTGAACAAAGCAGCAAAACAAAGGCAGTTTTATATGA
  AAGATTANAAGCCTGGAATAATCAGGCTTTTTAAATGATGTAATTCCCACTGTAAT
  AGCATAGGGATTTTGGAAGCAGCTGCTGGTGGCTTGGGACATCAGTGGGGCCAAGG
  GTTCTCTGTCCCTGGTTCAACTGTGATTTGGCTTTCCCGTGTCTTTCCTGGTGATG
  CCTTGTTTGGGGTTCTGTGGGTTGGGAAGAGGGCCATCTGCCTGAATGTAA
  CCTGCTAGCTCTCCGAAGCCCTGCGGGCCTGCTTGTGTAACCGTGTGGACAGTGG
  TGGCCGCGCTGTGCCTCCTGTTTGCCTACATGTCCCTGGTTGAGGCGCTGC
- Sequence ID 917

  NNCAGATTTTTTTTTTTTTTTTCAGNGTTAGACCATCTTTCAATTCCTGGAACAAAC

  TTAACTTTCCATGATATGTATTTTTTATACATTGCTGGATTTTATTTTGCTAATATT

  TTACTTAGGATTTAATTTTCTAAGTNGACCTATAATTNTCCTGTATAAAATTGCAT

  TTGTCACATTTTAGTATCAAGGTTGTCCTANCNCCATGAAATGGATTTANAATGGT

  TTATGTAANATAAAGTACATTTCTTCTAAAGGTTTGNGTGGATTAACTTTCAAATC

  TGCCANAGNGNGTTTTTTTCCTTTTTTTTTTTTTCATTTNAAGGGAGNGCAAGT

  ANCTTTCAAATNCTGATTTAATTTTTAAAATATTTNCAAGTNTNTTTANAGTTTT

- 236 -

 ${\tt TATTTNTTNTNGAANGTTAACATTTTTATANAAAANGGTNTTATCTTTTAAATTC}\\ {\tt TTTGACATCAGTTTCTTCANAATTCCTTCTTTTAA}$ 

Sequence ID 926

,15

20 .

10

5

Sequence ID 938

25

30

35

CAAGTTCCA

Sequence ID 947

GAGAGTGAAAAAATTCTGGTACAAATTGGGAAATTAGTATATAACAACATAGTGTT

AAATTCAATGGGAAAAGTTTAATAAGAGGATTTGGTATCAACTGGCTGTCCAAAGA

TAAAAATGGACCGTCCTATCACATACAAAATTGTTTTTTAGATAAAGATTTAAATA

5 CAGGCACTCCTTCATTTGCGTGGTGCACCTTGAGGTGTTGCAGAAATGATGAGAGC

TGAAACTGCAAAGCAATTTTAATACTTTATCTGTTGGAAATCTTATAGTTTTCCTG

TGACCGTTAAAATTTTCATTAAACTATTAAAAACACCCATGACTGGTCACAAATGT

ATTGGGAAATGGAAAAGAATTAATACACTAAAAATACAAAAAAATAGAAAATATTTA

AAATTATCTAAAAATTTGAAACATTAGAAAAATTGAGAACTAGGCAGGGCGTGGTG

10 GCTCACATCTGTAATTTTAGCCCTTTTGGGAGGCTGANGCAGGTGGATCACCTGANG

TCAGGAGTTCGAGACCAGCCTGCCAACGTGGGGAAACCCCGTCTCTACTGAAAATA

CAAAAATTANCCGGGCATGGTGGCACAAGCCTGTAATNCTTGCTNACCAGGANGCT

GAGGCAGGAGAATCACTTGAACCCANGANG

Sequence ID 949

GTTTCACATGAGAAGGTAGTATTATGTACAGTGACCTTGTTTAAAGTGTCNGTTTA
ATGTTACCACTAAGGCCCTGCCCCAGCTTTATCACCTGAGCACTAACAAGTGCTGT
GTGGAGTTCAGTCCATGCTGGTAACTNTTGAGTATTCAGTGGGTCTTTTAACAATT
ACCACCGTGGAGGANANAGCAAGGAAGAGAAATGCTGTGATCTTTTNCTGTTTTTA
ATTAGNGAAAGAGGGATTANATTAAACAAATGTTACAGAGNTGTGACTNTGATCCC
CCAGNGGTAAGCAATAATTGTANAGACTGGATTTNANAAGCCCTGAGAGTTTATTT
TCAACCTATNTATTATAGNNCAATCC

Sequence ID 1028

25 ACAAGGCTTGGGGGCTGGACTCCTTACTGCCTCTGGCCATACCCCCTCCTGGAG ATGGGGTCAAGGCACCAGGACTGA

10

- 238 -

Sequence ID 1071

NGATATAGTNCCGCATGGGAAAGATGANCAGGTATAACCNAGCNTNATATAGCAAG
GACTAACCCCCCTTCTGCATAATGAATTAACTAGAAATAACTTNGCAAGGAG
AGCCAAAGCTAAGACCCNGAAACCAGACGAGCTACCTAAGAACAGNTAAAAGAGC
ACACCCGTCTATGTAGCAAAATAGTGGGAAGATTTATAGGTAGAGGCGACAAACCT
ACCGAGCCTGGTGATAGCTGGTTGTCCAAGATAGAATCTTAGTTCAACTTTAAATT
NGCCCACAGAACCCTCTAAATCCCCTTGTAAATTTAACTGTTAGTCCAAAGAGGAA
CAGCTCTTTGGACACTAGGAAAAAACCTTGTAGAGAGAGTAAAAAATTTAACACCC
ATAGTAGGCCTAAAAGCAGCCACCAATTAAGAAAGCGTTCAAGCTCAACACCCACT
ACCTAAAAAATCCCCAAACATATAACTGAACTCCTNACACCCCAATTGGACCAATCTA
TCACCCTATAGAAGAACATATATGTTAGTATAAGTAACATGAAAAACATTCTCCTCCGC
ATAAGCCTGCN

Sequence ID - 1074

nt: 689

GGGAGGCGGAGGCTGAGCTGAGATCGTGCCACTTCATTCCAGCCTGGGCAA 15 TTTAAAGCTTGTCATTTTTATTTAGTAATAACACTCATTAGTGTAGTATCTATGA TGAACCAGGTTCTGCACAAAGTACCTTATGTTCATGGCCTCATATCGTCTTCTCCA AAACTCTGCAAGATAGGATTCATCACCACTTATAGGGAGAGATCTGAAAGTTTAAA ATTGTACCCAAGGTCACACAGCTGGTAAGTGCCAGAGCTGGGATTCCGTAGGGTGT 20  ${\tt TCANAGTGCCTCTCCTGCCGTAGGCTTATCACAAAAAGTCAAAGTTTGGTCATAAT}$ AAAGCCTGAAGTTTGGCAGGATTTAAAAATAGTCACCANACTTTTGAGTTGGAGCA TCCCACCTCACTGCTGTTCACCTTCTGTGGCAGGGAGAGTCATCATTTCCATTTCA GCTTGTGGAATATCTTGTCATTAACATTCTCATGCAAAAGCCATTTTATGGTGCCC 25 AATGAANATGGTTAAGCTACTGCCCCAAGCCTNTGGAAGCCTTCCTAATTTTGGAC TTGCACTATGCAAATTGNATAATATTTTCTCTACCCTAAGCCAAATATTTTCTTCA CTTTTCATTCATTCTAC

Sequence ID 1081

- 239 -

 $\label{eq:GTGTAACAATTATGCCAAAAGACATCCAGCTAGCACGCCGCATACGTGGAGAACGT\\ GCTTAAGAATCCACTATGATGGGAAACATTTCATTCTC$ 

Sequence ID - 1083 nt: 198

- Sequence ID 1099 nt: 561  ${ t TGCATGCTTGTGGATTGGAAAAACTTTGGAGACTGATTACTTTTCATTATATATGT}$ GTCACAGTGAAACAGCTTTTATGTGTCATGTAAGATTACTGCTTGCCTCTCTAAGG  ${\tt AAGGTCGTGACTGTTTAAATAGACGGGCAAGGTGGAACCTTTTGAAAGATGAGCTT}$ TTGAATATAAGTTGTCTGCTAGATCATGGTTTGTATTGAACTAACAAGGTTTGCAG 20 ATCTGCTGACTTATATAAAGCTTTTTGATTCCTACTAAGCTTTAAGATTTAAAAAA TGTTCAATGTTGAAATTTCTGTGGGGCTCTATTTTTGCTTTGGCTTTCTGGTGAGA  ${\tt TTGATTTAAGAGACTAAGGGAATTTACAAACTAAAGATTTTAGTCATCTGGTGGA}$  ${\bf AAAGGAGACTTTAAGATTGTTTAGGGCTGGGCGGGGTGACTCACATCTGTAATCCC}$ 25  ${\tt AGCACTTTGGGAGGCCAAGGCAGCAGCAGCATTGAAGGAGTTCAAGACCAGCGTG}$ G

Sequence ID 1109

TTTGNCGGTNTTGGANNNNNANAANTTTCTTCCANNCNTNACNTNTTGGTGGNCTA
AATTAANATGGNTTTNGNGGGTTCNTTNCTNNNTNNNNCATGGGANANAATTNATT
NTCNTNCNNNTTCCTTNNCCCTNAANCTACCTTCCCCCNATTTTCTCCCCCTNTTCN
TNAATTANCATCCTCTCCNCNTANNTCNANACNTTAATGGCAANACTATCTAATAN
CNANNATAANANCTCCTGTNNNCCACATNTCTTATTNNNCGCNNCANGTTNCANNC

35 CCNCAGAGTNAACTCATCCTCNNCNNAANTTCATATCGTGNNCTNTNNNCNNTNGC
GCGANATATTAANNANACCNGTANNTNNNANACANNANNTNNGNAANAANCCTTCT
NANNTTTTAGCNTCNNGCNNTAACNNNNNTCTTNGTGNNNNCNCAGCTTTCNCNNC

ATNATNCTNCNNCGAANTNTCANNCNTCTCCNCTTNAATGNNTTCCCATGNATTAA
NTNCCTCGNNNANAGCACTATCGTNNNNGAGNNNATTATNGNCNNTTTACNTCATG
TGGTCCANTNNCGTTNGNCGCNNNNAATNTTCGTNNNNCNN

## Sequence ID 1125

20 -

25

NGACTGGCTCCCGAAAAGAAGGGTGGCGAGAANAAAAAGGGCCGTTCTGCCATGGA CGAAGTGGTAACCCGCGAATACACCATCAACATTNACAAGCGCATCCATGGAGTGG GCTTCAAGAANCGTGCACCTCGGGCACTCAAAGAGATTCGGAAATTTGCCATGAAG GAGATGGGAACTCCATATGTGCGCATTGACACCAGGCTCAACAAANCTGTCTGGGC CAAAGGAATAAGGAATGTGCCATACCGAATCCGTGTGCGGCTGTCCANAAAACGTA ATGAGGATGAAGATTCACCAAATAAGCTNTATACTTTGGTTACCTATGTACCTGTT ACCACTTTCAAAAAATCTACAGACAGTCAATGTGGATGANAACNAATCGCTGATCGT

- 241 -

Sequence ID - 1148 nt: 587 TGAAAAATAAAGTTTTTATGTATATTCTACATATGTATATGTTGGTAGAAAGCAAA AACGCTAGGTAAAAATAAATGTAATACAATTTTAGCTATGAACCAAAAAACCATTT GTGGTGTGGATGCAAGAAAGTCTGGATGGGTGCAGAGTTCTCCATGTTTCACTTCT GACATTTGAAAATACGCAGTTTGCATTTGATACGTCAAATGTTATTTTAAGAAAA 5 CCAATAAAATCATTAAAACCGAAAAGGCAGTTTTGCTTGTTTTTACCTTAGTTGGA CCCCTTTAGAGCTACGAAACATGTCAATTTTACTTTTCTCCAGCTTTTTGGAATCT TATCTAAATTACCATGTAGAGTTCTGCATAGCTTCAAATTCTCTTAGCCAATGTGG  ${\tt TCTGTAAGTGTCTATCGATGAATTTCACCGTTAATTGCCGTAGTATACTGTCCTGT}$ 10 ACCGGATGTGAAGAGGAGCAACTCTGCACAGTGCACTGGTTGCTCCCATGGTAGGA ANGAATGGCTTATCAATGGTCGGATTT

Sequence ID - 1160 nt: 650 GGAGGATGGAGCAGTGAGCGGGTCTGGGCGGCTGCTGGCAGCGCCATGGAGACGGT 15 ACAGCTGAGGAACCCGCCGCCGCCGGCAGCTGAAAAAGTTGGATGAAGATAGTTTAA CCAAACAACCAGAAGAAGTATTTGATGTCTTAGAGAAACTTGGAGAAGGGTGAGTG TAAAGAAACTATAGGTAGGTCATTGGGTCCCAGTCTTTTTCCTGCCCCAGAAGAAG CAGAAGGATATGAACCTTTCAGCATTGTTCTAGGTGGGGTGGAAGGTAAATTTACA GCTTGTGATGTCCTTCTCGCTTTACTCCAATCCCTATTATAGACAGATTTAGTGA 20 TTCCTGGTCTTTTAACACGAAGAATATCTATTGTTTTCTCTTTTGTAGGATCTGT ATGATTTATCTACTTAACAGATAGCACTAATTAGATTAAAATTCTATAAGAAACT TTTTAATTTGCTGTTCATAATTTCTGATTGGTATGCAATAACTGTTTCAATGAAAA 25 AAGCACTATCACCACCTTCACAGCTACTTAGGAGATCCACAATCCTGGGTTGGGAG

CCAGTGGATTTCCTGAAACACAGATTTGTTAATG

Sequence ID - 1172 CCACAATAATAAGAGAAAAACAGGAGCAAAAGGATATACAAAACCACCAGAAAACA nt: AATAACAAAGTGACAGGAGTAAGTCCTTAACTGGCAATAATAACCATGAATCTAAA  ${\tt TGGATTCCATTTCCCACTTAAAAGATAAAGACATGCTGAATGGATAAAAAGCTGTC}$ 5 TGGAAAGAGAAGCATGGGAAAAGATACTCTACTCAAATGAAAACAAAAACCAAAC AAAGGTGGCTATTCTTATATGAGATAATACAGACATTAAATCAAAAACTGGAAACA AACACAAAGTCATTGTATAATGATGAATTCAATTATATCATGATGAATTCAATTAT ACCCAACACCAGAGCATATAAATATGTAAAGGAAGATAAAGGGAGTCCTGTGATCA 10  ${\tt CAATAATAGGGTGACATTAACACCCCCTCTCACATTGGACTGATCATCTAGAA}$ GGGAGAAAAAGCTTTATGATTGGAAAAGCCAT

- 15 Sequence ID 1178  ${\tt ATTGTGTTGGCCACCCGGGAATTCGCGGCCGCGTCGACCTACGCACACGAGAACAT}$ GCCTCTCGCAAAGGATCTCCTTCATCCCTCTCCAGAAGAGGGAGAAGAGAGAACACA AGAAGAAACGCCTGGTGCAGAGCCCCAATTCCTACTTCATGGATGTGAAATGCCCA GGTGAGGAGACGGCTTGCTGGTAGTGGGAAAGCACTGGACCTCAACAGTTGGAAAA  ${\tt TGTTGTAGTGTTAGCTGTCTCGTATCCTTGAAGCTGTGCAGCAGCTTCAGTTTCTT}$ 20  $\tt CGCCTGTGGAAAATATTTTCCCTGATACTCTTAAAATTTGAATGTATGAGACTGGC$  ${\tt AAAGTTTTGCATCTTAGGAGGAGTGATTCATTTCACCGTGATCTCATCACATTT}$ CACATACAACCCCTACGTTTTTTGTGTTTGGGAAACAATGTAATGGATGATGAGTT  ${\tt GGGCATAAGTGCAGGAAAGACGGGTGTAATAGAGGAAAAAATGTTATCTGCTTTT}$  $\hbox{\tt CTTTCAGGATGCTATAAAATCACCACGGTCTTTAGCCATGCACAAACGGTAGTTTT}$ 25  ${\tt GTGTGTTGGCTGCCACTGTCCTGCCAGCCTACAGGAGGAAAAGCAAGGCTTA}$ CAGAAGGATGTTCCTTCAGGAGGAAGCAGCACTAAAAGCACTCTGAGTCAANATGA GTGGGAAACCATCTCAATAAACACATTTTGGAT
- Sequence ID 1180 nt: 622

  CTTTTCCTCCCGCTGTCCCCCACGGGAGGGGACTGCTCTCCCCCGCTGCATCCTTT

  CTGTGAGGTACCTTACCCACCTCAGCACCTGAGAGGGTGAAATAGAATTCTAACCT

  CGACATTCGGGAAGTGTTTTTGAGAAGTCTCGGTCGGTAAGGGAAGTCTTCCAAGT

  CCGTGCAGCACTAACGTATTGGCACCTGCCTCCTCTTCGGCCACCCCCCAGATGAG

  GCAGCTGTGACTGTCAAGGGAAGCCACGACTCTGACCATAGTCTTCTCAGCT

  TCCACTGCCGTCTCCACAGGAAACCCAGAAGTTCTGTGAACAAGTCCATGCTGCA

  TCAAGGCATTTATTGCAGTGTACTATTTGCTTCCAAAGGATCAGGCCCTGAGAACA

10

30

35

- 243 -

ATGACCTTATTTCCTACAACAGTGTCTGGGTTGCGTGCCAGCAGATGCCTCAGATA CCAAGAGATAACAAAGCTGCAGCTCTTTTGATGCTGACCAAGAATGTGGATTTTGT GAAGGATGCACATGAAGAAATGGAGCAGGCTGTGGAAGAATGTGACCCTTACTCTG GCCTCTTGAATGATACTGAGGAGAACAACTCTGACANCCACAATCATGAGGATGAT GTGTTG

Sequence ID 1182 CATTGTGTTGGCNCCCGGGAATTCGCGGCCGCGTCGACTTTTTGTGTTTTGGAG CAGAAATACTAAAGAAGATTCCGGGCCGAGTATCCACAGAAGTGGACGCAAGGCTC TCCTTTGATAAAGATGCGATGGTGGCCAGAGCCAGGCGGCTCATCGAGCTCTACAA 15 GGAAGCTGGGATCAGCAAGGACCGAATTCTTATAAAGCTGTCATCAACCTGGGAAG GAATTCAGGCTGGAAAGGAGCTCGAGGAGCACCGCCATCCACTGCAACATGACG  ${\tt TTACTCTTCTCCTTCGCCCAGGCTGTGGCCTGTGCCGAGGCGGGTGTGACCCTCAT}$ CTCCCCATTTGTTGGGCGCATCCTTGATTGGCATGTGGCAAACACCGACAAGAAAT 20 CCTATGAGCCCCTGGAAGACCCTGGGGTAAAGAGTGTCACTAAAATCTACAACTAC TACAAGAAGTTTAGCTACAAAACCATTGTCATGGGCGCCTCCTTCCGCAACACGGG CGAGATCAAAGCACTGGCCGGCTGTGACTTCCTCACCATCTCACCCAAGCTCCTGG GAGAGCTGCTGCAGGACAACGCCAAGCTGGTGCCTGTGCTCTCAGCCAAGGCGGCC 25 CAACGAGGACCAGATGGCTGTGGAGAAG

Sequence ID - 1183 nt: 479

CGTGGCAGCCATCTCCTTCTCGGCATCATGGCCGCCCTCAGACCCCTTGTGAAGCC

CAAGATCGTCAAAAAGAGAACCCAAGAAGTTCATCCGGCACCAGTCAGACCGATATG

TCAAAATTAAGCGTAACTGGCGGAAACCCAGAGGCATTGACAACAGGGTTCGTAGA

AGATTCAAGGGCCAGATCTTGATGCCCAACATTGGTTATGGAAGCAACAAAAAAAC

AAAGCACATGCTGCCCAGTGGCTTCCGGAAGTTCCTGGTCCACAACGTCAAGGAGC

TGGAAGTGCTGCTGATGTGCAACAAATCTTACTGTGCCGAGATCGCTCACAATGTT

TCCTCCAAGAACCGCAAAGCCATCGTGGAAAGAGCTGCCCAACTGGCCATCAGAGT

CACCAACCCCCAATGCCAGGCTGCGCAGTGAAGAAAATGAGTAGGCAGCTCATGTGC

ACGTTTTCTGTTTAAATAAATGTAAAAACTG

- 244 -

Sequence ID - 1185 nt: 628 TGATGATGTTGATTGGGTCATGTCAGATTTAGACAGTGTTGTGTTTAAGATAAATG TTTAATGGCTCTTAGCAGTGTTCATGCCTCCCCTTTTCCCCCTGATACTTTAAAAAC AGAATATACAGAAAAGGGGAGTTGGGTGAAGAATCACCATATTCTCATTACCAGAG 5  ${\tt TAGTGTCTACCAGCTGTTTTCACATTTTTCTGTTTCCTTTCTGTCCTTGGAATCCTT}$  ${\tt TTTTTAGATCCTTGTAATACTAGTAAAGATATTCCACTCTGTGTTAAGCATTTT}$ TCCATTTTGCTCCATGGTCTTCATAATGCCCTGTGGTCCTTTATTAAGGGGATGCA  ${\tt CCATGTAGAGGTGAAAGGCTTTCCTTGACTTGGCCACCATTTCTGTATTTTCCTTA}$ GAGGAGGAGGTTTCCAACATTTCTTTTTAGAGACAGAGTCTCGTTCTGACACGCA 10 GGCAGGAGTGCATGATAACAGCTCACTGCAGCCTCGAACTCCTGGGCTCA CACCCAGCTAAT

Sequence ID - 1188 nt: 599  ${\tt GGGAGACAAGCCCAGCCTTTCGGCGAGNATACGTCTAACCCTGTGCAACAGCCACT}$ ACATTACTTCAAACTGAGATCCTTCCTTTTGAGGGAGCAAGTCCTTCCCTTTCATT TTTTCCAGTCTTCCTCCTGTGTATTCATTCTCATGATTATTATTTTAGTGGGGGC GGGGTGGGAAAGATTACTTTTTCTTTATGTGTTTGACGGGAAACAAAACTAGGTAA 30  ${\tt AATCTACAGTACACCACAAGGGTCACAATACTGTTGTGCGCACATCGCGGTAGGGC}$ GTGGAAAGGGCCAGAGCTACCCGCAGAGTTCTCAGAATCATGCTGAGAGAG CTGGAGGCACCCATGCCATCTCAACCTCTTCCCCGCCCGTTTTACAAAGGGGGAGG  $\tt CTAAAGCCCAGAGACAGCTTGATCAAAGGCACACAGCAAGTCAGGGTTGGAGCAGT$ AGCTGGAGGGACCTTGTCTCCCAGCTCAGGGCTCTTTCCTCCACACCATTCAGGTC 35 TTTCTTTCCGAGGCCCCTGTCTCAGGGTGAGGTGCTTGAGTCTCCAACGGCAAGGG AACAAGTACTTCTTGATACCTGGGATACTGTGCCCAGAG

10

30

35

Sequence ID 1189

GGGAGACAAGCCCAGCCTTTCGGCGAGATACGTCTAACCCTGTGCAACAGCCACTA
CATTACTTCAAACTGAGATCCTTCCTTTTGAGGGAGCAAGTCCTTCCCTTTCATTT
TTTCCAGTCTTCCTCCTGTGTATTCATTCTCATGATTATTATTTTAGTGGGGGCG
GGGTGGGAAAGATTACTTTTTCTTTATGTGTTTTGACGGGAAACAAAACTAGGTAAA
ATCTACAGTACACCACAAGGGTCACAATACTGTTGTGCGCACATCGCGGTAGGGCG
TGGAAAGGGCAGCCAGAGCTACCCGCAGAGTTCTCAGAATCATGCTGAGAGAGC
TGGAGGCACCCATGCCATCTCAACCTCTTCCCCGCCCGTTTTACAAAGGGGGAGGC
TAAAGCCCAGAGACAGCTTGATCAAAGGCACACAGCAAGTCAGGGTTGGAGCAGTA
GCTGGAGGGACCTTTGTCCCCAGCTCTCCCCACACCATTCAGGTCT
TTCTTTCCGAGGCCCCTGTCTCAGGGTGAGGGTGCTTGAGTCTCCAACGGCAAGGGA
ACAAGTACTTCTTGATACCTGGGATACTGTGCCCAGAGCCTCGAGGAGGT

## Sequence ID 1190

#### Sequence ID 1191

WO 2004/046382 PCT/GB2003/005102

- 246 -

AAAGAAGATAACTAAAAGTTAAAAGTCGTTGCATGTTTTTGTTGCAGCATACCCTT CTTTCAGGCTACCGAATAACCTTGATTGACATTGGATTAGTAGTAGAATACCTCAT TGGTAGAGCATATCGCAGCANCTACACTAGAAAACAT

5 Sequence ID 1192
GTCTGGAACTCCAGACCTCAGGTGATACCCCTGCCTCAGCCTCCCAATGTGCTGGG
ATTACAGCTGTGAAGCCACCGCGCCCGGCTGCTGTGATAGTTGAGATGTAAACCAA
AAATAAAATTCTAAGCCACCCAATCCGACTGAATGGACCCTTCCTGTTGAGCAAGG
ACATTCCAAAAGTAAACTGAAAAGACCAGCTTAGGCCATGATGGGAAGGGGAGGTGT
CAACATGCCTCATTCTACCTTCCTCCCTCTGGAATCCAGACACAACTGACCAGCAT
TAACATTAAAACAGAGATCTTAAGCTGGGCACGGTGGCTCATGCCTGTAATCCCAG
CACTTTGGGAAGGCCAAGGTGGGATCACCTGAGGTCGGAAGTTCAAGACCAGCCTGG
CCGGTATGGTGAAGCCATGTCTCTACTGAAAATTGGCCGGACATTGTGG
TGCA

15 Sequence ID 1193

 ${\tt TNCNTTTTTTTCCCNCGGGAAAGCGCGCCATTGTGTTGGTCCCCGGGAATTCGCG}$ GCCGCGTCGACGAGAAATGGCTTGAACCCAGTAGGCAGAGGTTGTAGTGAGCCCAG AATNGGNCACCTGCACNTTTANCCNTGGGTGACAAANTGAAAACTTTGTCTNAAA AAAAAAAAAAAATTTTAANTNAAATNAAAANCCTTTNCNTTNTTTTTNAAAN 20 GGGGCCNANNCCCCNTTTTANAAAANCCNGNTTTTNAAAAAANTTTTTTNCCCNCN NTTNGGGGGGGGGTTTTTNANCNNTNTTNGGGGGGGNNCCCCTNTTANNACCNNC GGGNNGCCCCCNNCCTTTNGGGGGGGGGGTTTNNGNAAANNACTTTTNAAAANNA 25 AGGGNNGGGGGNANATNNCCCCCCCNGGNTTTTTTTTTTAAAAANTNAANNGGGGG GGGNNNCTNANTNGGGGCNCCCANNGGGGGNTTANAANNATTTTCTNCCCAAACCC TTTTNGGNAAANCCNNGGGGGGNTCCTTTTTNAAANNNNCCCCCAAAAAAAANTTT 30 TTTTNTTNTTTTTTCTCTNGGGGNCCNNANTTNTANANTTTTNCNCCNAAAAAA ANGGGNCCCCTTTTTTTNCNGGNNGGNNCCCAAAANNTTTTTTTTTNAAAAAAAAA AAAA

Sequence ID 1195
GTTCGTGACNTTCGGAGCTACCTGACAGAGCAGAGTCAACCAGGNTCTGCCCAAAG
AGAGTGTTAGGCCTGAGCTTGAGAGCCCTGGAGAGACGTGTGCACAAAATGTGACC

 $\label{totaga} TGAGGCCCTAGTCTAGCAAGAGGACATAGCACCCTCATCTGGGAATAGGGAAGGCA\\ CCTTGCAGAAAATATGAGCAATTTGATATTAACTAACATCTTCAATGTGCCATAGA\\ CCTTCCCACAAAGACTGTCCAATAATAAGAGATGCTTATCTATTTTA$ 

- Sequence ID 1197

  CCGCCAACATGGGCCGCGTTCGCACCAAAACCGTGAAGAAGGCGGCCCGGGTCATC
  ATAGAAAAGTACTACACGCGCCTGGGCAACGACTTCCACACGAACAAGCGCGTGTG
  CGAGGAGATCGCCATTATCCCCAGCAAAAAGCTCCGCAACAAGATAGCAGGTTATG
  TCACGCATCTGATGAAGCGAATTCAGAGAGGCCCAGTAAGAGGTATCTCCATCAAG

  CTGCAGGAGGAGGAGAGAAAAGGAGAGACAATTATGTTCCTGAGGTCTCAGCCTT
  GGATCAGGAGATTATTGAAGTAGATCCTGACACTAAGGAAATGCTGAAGCTTTTGG
  ACTTCGGCAGTCTGTCCAACCTTCAGGTCACTCAGCCTACAGTTGGGATGAATTTC
  AAAACGCCTCGGGGACCTGTTTGAATTTTTCTGTAGTGCTGTATTATTTTCAATA
  AATCTGGGACAA

Sequence ID 1198

CAGAGGTGGGAGGATTGCTTCAGTTCAAGAGTTTGAGACCAGCCTGGGTAACATGG

CGAAACCCTGTCTTTACAAAAAATGCAAACCTTTGCCGCATGTGTTGGGGTGCGCC

TGTAGTCCCAGCTTCTCGGGAGGCTGAGGTGGGGGGACCACCTGAGCCATGGAGGT

30

TGAGGCTGCAGTGAGCCGTGATACCACCACTGTACTCTAGCCTGGGCCATAGAGTG

AGACACCCTGCCTCAGAAATA

5

10

15

Sequence ID - 1201

nt: 613

30

35

GGAATTCGCGGCCGCGTCGACCTCTGCTCGAATTGACAGAAAAGGATTCTGTGAAG
AGTGATGAGATTCCATCCATGCTGACTTTGAGAATACATGTTCCCGAATTGTGGT
CCCCAAAGCTGCCATTGTGGCCCGCCACACTTACCTTGCCAATGGCCAGACCAAGG
TGCTGACTCAGAAGTTGTCATCAGTCAGAGGCAATCATATTATCTCAGGGACATGC
GCATCATGGCGTGGCAAGAGCCTTCGGGTTCAGAAGATCAGGCCTTCTATCCTGGG
CTGCAACATCCTTCGAGTTGAATATTCCTTACTGATCTATGTTAGCGTTCCTGGAT

30

35

Sequence ID - 1203 nt: 692 TGCAGAGGGGTCCATACGGCGTTGTTCTGGATTCCCGTCGTAACTTAAAGGGAAAC TTTCACAATGTCCGGAGCCCTTGATGTCCTGCAAATGAAGGAGGAGGATGTCCTTA 10 AGTTCCTTGCAGCAGGAACCCACTTAGGTGGCACCAATCTTGACTTCCAGATGGAA CAGTACATCTATAAAAGGAAAAGTGATGGCATCTATATCATAAATCTCAAGAGGAC CTGGGAGAAGCTTCTGCTGCAGCTCGTGCAATTGTTGCCATTGAAAACCCTGCTG ATGTCAGTGTTATATCCTCCAGGAATACTGGCCAGAGGGCTGTGCTGAAGTTTGCT 15 TGTAACACAGATTCTCCTCTGCGCTATGTGGACATTGCCATCCCATGCAACAACAA GGGAGCTCACTCAGTGGGTTTAATGTGGTGGATGCTGGCTCGGGAAGTTCTGCGCA 20. TGCGTGGCACCATTTCCCGTGAACACCCATGGGAGGTCATGCCTGATCTGTACTTC TACAGAGATCCTGAAGAGAT

Sequence ID 1204

Sequence ID 1205

WO 2004/046382 PCT/GB2003/005102

- 250 -

TNNNNNTNNCNNCNANTAANNCANNTCNANNNNANNNAATTACTTNNANGTNNNTC ACN

Sequence ID - 1207

nt:

642

والإسرائيج وإلان المراويج الجرائية والمساوم والمساوم والمساوم والمعاومة والموادات

Sequence ID 1208

20

25

Sequence ID - 1209

nt:

620

CTCTCCTGTCAACAGCGGCCAGCCTCCCAACTACGAGAATGCTCAAGGAGGAGCAG
GAAGTGGCTATGCTGGGGGCGCCCCACAACCCTGCTCCCCCGACGTCCACCGTGAT
CCACATCCGCAGCGAGACCTCCGTGCCCGACCATGTCGTCTGGTCCCTGTTCAACA
CCCTCTTCATGAACACCTGCTGCCTGGGCTTCATAGCATTCGCCTACTCCGTGAAG
TCTAGGGACAGGAAGATGGTTGGCGACGTGACCGGGGCCCAGGCCTATGCCTCCAC

35
CGCCAAGTGCCTGAACATCTGGGCCCTGATTTTGGGCATCTTCATGACCATTCTGC
TCGTCATCATCCCAGTGTTGGTCGTCCAGGCCCAGCGATAGATCAGGAGGCATCAT
TGAGGCCAGGAGCTCTGCCCGTGACCTGTATCCCACGTACTCTATCTTCCATTCCT

CGCCCTGCCCCAGAGGCCAGGAGCTCTGCCCTTGACCTGTATTCCACTTACTCCA
CCTTCCATTCCTCGCCCTGTCCCCACAGCCGAGTCCTGCATCAGCCCTTTATCCTC
ACACGCTTTTCTACAATGGCATTCAATAAAGTGTATATGTTTCTGGTGCTGCTGTG
ACTT

5

10

20 .

25

30

15

35

Sequence ID - 1212 nt: 374
AGAGCAGCAGCCATGGCCCTACGCTACCCTATGGCCGTGGGCCTCAACAAGGGCCA

20

25

30

Sequence ID - 1213 nt: 567  ${\tt GAATTATTGACTTTGAATTGCATTTCAGTACCATGAAGTCAAAGTCAGTGGTGTAT}$ 10 GTGAGTGCAGAÄAT,CCTGTCAATTCGTCACTTGTGGACAACCTGCAGCTTGCCACA TTGGAAATCCTGAATGGGCTTGGAGACATTAAGGGAGAACTGCCTCCCTGGACCAA GGCAGAATTCAATAGAACCAGCAAGAAATTTTCCTATGAATGGGAAAGCAGGTGGC AGGGGGCAGGGTGGAAAAGCTTTGTACAGGAATTGTGGAAAAGCTTTTGCATTAT 15 CTCTAGTCTGAAAGTCACATTTCTCAGTTCCTTTCCACTCTCTTCTGTCAACTTGC TGTGAGTAAATGACATCTGTCACCTGTGACACGGGCCAGGGACTATCACCATATGG CCCCCACACATTATCTAGTACCAGCCTGCCTGGGCCATGCCTTTTCCAGTCACTGT ACCAGCC

Sequence ID - 1214 nt: 620
CTCTCCTGTCAACAGCGGCCAGCCTCCCAACTACGAGAATGCTCAAGGAGGAGCAG
GAAGTGGCTATGCTGGGGGGCGCCCCACAACCCTGCTCCCCCGACGTCCACCGTGAT
CCACATCCGCAGCGAGACCTCCGTGCCCGACCATGTCGTCTGGTCCCTGTTCAACA
CCCTCTTCATGAACACCTGCTGCCTGGGCTTCATAGCATTCGCCTACTCCGTGAAG
TCTAGGGACAGGAAGATGGTTGGCGACGTGACCGGGGCCCAGGCCTATGCCTCCAC
CGCCAAGTGCCTGAACATCTGGGCCCTGATTTTGGGCATCTTCATGACCATTCTGC
TCGTCATCATCCCAGTGTTGGTCGTCCAGGCCCAGCGATAGATCAGGAGGCATCAT
TGAGGCCAGGAGCTCTGCCCGTGACCTGTATCCCACTTACTCCT
CGCCCTGCCCCCAGAGGCCAGGAGCTCTGCCCTTGACCTGTATTCCACTTACTCCA
CCTTCCATTCCTCGCCCTGTCCCCACAGCCGAGTCCTGCATCAGCCCTTTATCCTC
ACACGCTTTTCTACAATGGCATTCAATAAAGTGTATATGTTTCTGGTGCTGCTGTG
ACTT

10

25

30

35

Sequence ID 1218
CTCACTTGGTGGGTGAGCCTCCAATGACTACACCCAAGGAGGATTTAACACAGGGA

10

TTTTATGACTTGCAACAAGTCAGGAGGACATGGGGTTGGGGTAGTTCAGCAGTGCC
TGTCTGAACAAAGGTGAAAATTGGGCTTTTTATTGGGCTGATCAAGGGGGAGTAAAG
GCAGCCAGGAGCAGTCGCCTGTCATGCTTCTACCTATATTGCATGTATAGAAAAGG
GAAAATAAACTCCTTCCTGGGCAGGGTTTTAGTATGCTAAGGAGGGGAGTTATTCA
ACTTCAATCCAACTCAAGCATCAGCATTGCTGCGTCCATCCCAGTTTTGTTTTGCT
GGGGCTGAACTTCTTCCTATAACTTTTTGAAACAACAAGAACTCAAGGTGTGACAG
TTACAAGTGGGCCCTTTTTCACAGTGTGTACCTAAACACGTGAGGACCCTGGATTA
CAGAATGACAGACTCGAAGTGACTCAAGTTCCGGTTGTTCATCTTTAGATGGTAAA
GATGGCTGTACGTACTATCCTTGCTTATTTCCAATCTATTGTTTAAACTCTTGTAT
ATGTAATACCGCAGAGGCTAGAGATACAACCTTTGACCAAATGAGTGAATTCAAGT
AATCCATTACTAATGTGATCTGGAAACAACATGGTGTTGAATGT

25 Sequence ID 1220 ... GANNNGTGCGATANNATGNNTGTCTTTTTTTTAAAGTNTTTCNNATNGNAGNGAAN CCCCCNNANNTNNCATAANGAGAGATNACTACNGTACANATAGNGNCANACNGATA GTAGTANCAANATTGTNTTAGCTANATNANTCAATAGATATCNAGATANAANAANA NCNNGGATATACAGCGATGTNTNANNGGNNNNNNNANGGAACGAACATCNACNTTA ANNATAAGCTNGNGGAGAGAGACANGTANGTTATANANNAGAATNGNAGTAGGNGT 30 GATCATAATAGNNNNNANNTANTATATANGATNTTANTGNNCTNTNNTNNGTTTAT CNNNAATNTCTATNCTNGAGAGNAGCNNNATNNNNAGGCGANGANATTGGGNNNTN CTCNTNATAGANANCTGGTGTCNNANAANTACNTCATCTATTNANCTCTCACNANA TGGNANNATANAGNAGNGNNNTNNANAGGANTANGCATAGNGNNTNNCTNAAACAA AANNNATAAGANNTCTCGNNAANANGGGCCTNTNNTNTAGCGAGGNNTTANTTTNT 35 ATANTTNTTCNCTCTTNNAATANNTANGATANATGANCTNGNNGTGATANATANNN NNTACNGTNAANNTNTANTCNTATAATAGATANAAATATAGGATNTTNCTCTGGCN

10

- 255 -

GGTNGAANANTTNNTNCNNTTTNAATAATGNTGTTAGNGACNGNGNTNTNANANNN NNTTAGAAAGGTACTCTATATACTNNTATGNTNCGGCNNATAATANAACAGATGTT TGTATNAATANAAAAAAAGGTCNNTTTCGNCAAGAGAANNNTGNCTGGTNATAGAA TTAGCATAANTTANNTANTATGATNNANTNNTNCTACNANTNTTAGCNNTTNGCAG NAGTCATTNNGNATNTATNNNGNNTANTAGTNANTTGGGNCTNNTNCAGANTATAT TNTGNGAANATGAANNTACGNANTCCTNNGNANTATNATNNTGANTANGANAANCN ANANNTNTTNTANNANTGNCTATANATTGCCNNGATANATTNTNNNAATGAANCGA TAGCCCGCNCTAAGGANNTNNGTNANNTAAANNTCTCAGATAANNTACNTNTTNNT TATTAANCNANNATCACANTATANCNGNGACANNNGCGANANTATATGTATGNNAN TATNACNGNTCCMNNCCGNGAANNTANTCNTANNAGGCATTCNGNNGAGCTNTTCT NCTAGACNATTTNNANTGAAANNATGCNGNNAAAAACGACNNNCTTNAANTTNTGT CTACANTCCGCNNTNTTTNTACAGATNGCAGNTAAGNNNANTNANNGCTCTCANCT NGCTNNNACT

15 Sequence ID - 1221 nt: 741 AAGCAGAANTNTCTCTAAAAACATTATCTCCTTAAAATCTTGAGGTGCATATNAGA GCCACAGGCAATCTCTGACATATAAAATTGCAGTACAGGCCTTTCAAATTTGGCAT TTCACTGGTACAATACAACAACAAGATATATAATAACTGTACAGTGCCTAGACAT TCCAGTAAGAACCATTATTTTCTTTAATGTAGAATGATTAATACATATTCTACAAG 20 GGGCAGTAAGGTTAGTAATTCTATAGGGTATGTCCCGACATAATTTTCAAATTGTA CAATAACACAACAACTTTGTTAAGGCCATGTTTTATTTGCTGATTAATGGACAAA AGGCAATGTAATTTATTTTCAAGTATTTTCTTGAAAGTCTGTGCTCATAAAAATCA TGAAAAGTTGGAAAGACTGTTAAATCACTGAAACTTCAAATATATCTTACACAATC TTGTTTGTACAAAAATACAAGTTAAATATAAACATAAAGCAATCATGGTAATTTTA 25 TGCAAATCTGTTTTATGTGATCATCAGTTATATAAAAGTTTCTCAGTTCTGTTA TTTGTGAAAAGATCAATACCAGATTGAATGACTACCTATTGGCAAAGGGCCCTAAA AAGCTTACTTTAGCACTCATCTTTTACATGGTTAAATGCATTTCCTAATTTGAGAT CACCTAAACACTGGAAAAGAAAAAAATGAAAGGGCAGTATGTCCATAAACCAACA AATAATTTGGCTG

30

35

TTTAAAGAAAGGTGAGATTGGCTTGGTTCTTCATGAGCACATTTGATATAGCTCTT TTTCTGTTTTTCCTTGCTCATTTCGTTTTTGGGGAAGAAATCTGTACTGTATTGGGA TTGTAAAGAACATCTCTGCACTCAGACAGTTTACAGA

- 5 Sequence ID 1226  ${\tt GGTTTTTATACTTGCCATGAAACTGTTCTTTGGGATATTATTTTGTTCAGGTTCCC}$ CACTTGGACAGCAGAGGGGGTGACTCTGCCCATCCCTGCCACTGGTAGCCAGGCGG  $\tt CTCCTAGCCATGCAGGCCATGTCTGCTAGAGCTTCCAGCGCAGTGGTCCTAATTCT$ 10 GTCTGAATCCGGCTGAGGGGTGCAGCCTCCTGTTACTGCCCAGGGAAACACCCCAGA TGGCAGGGTGGGTGACTCCAACCACCTCTGCCTGTGGTAGCCAGATGGGCCACACC CCTAGCTGAGCAGGACTTGCTGGTTTGGACAATGCCCAAGCAGGGAAGAGCCCTCA 15 TTCTCTTATCACTGACAGAGGTGAGATGTCCGANTTTGTANGCTGGTGGAGGAGTG AGGTGGAGGAGGTATGCCTCT
  - Sequence ID 1228
- - Sequence ID 1230 nt: 741

10

35

Sequence ID - 1231 nt: 203

TTGAGGAAGGGTCTACTGTCTTTTTAAATGGCACAATTTTAAGAGGTTTGAGAGGT

ACAGTCCCTTAACCTGCCACGGGAGAGGGGCCCCCAAACTTTCTCCCCCCACACT

TCTGGTTTTCTGTGTGGAGGGGGGAGCAGGGATATCTAAGCTGTGGTGTAAAGGGT

AGGAGAGATGCTGGAGGTGGGGGGTGCTGTTCTA

# Sequence ID 1239

15  ${\tt TTTCCTCGGGAAGCGCCCATTGTGTTGTTGCTACCCGGGAATTCGCGGCCGCGTCGAC}$ TACAAAATATAGCAATACAGNGAACTTCACCAAATCCTAAATATTCAGTACCTGA ACTGGCTACAACACCGNGTGCACACCCAGTTCCTGCAGAATCTCTTGCAGATATGG GAGAGTCAGCCAGTGAAAAGATCCATTTCTTGGGAATCCTTGTCAACAAGACCAGT TCAGAAATCCAGGATATATAGAAGCCTACTGTAATTTAAAAACAGTAACAAAAACC 20 . CCAACAAAACCCAAATCAACAAAGACCAAGATAAAGGNGTGATAAACATTAATTGT AATGGTTTTCCTTTACATGCAATACATGCATTTTAAAATCACTAAGAAACACGAAA TTTATACTATTAAATTATATATTTTTTCCATACAAAAGCACACAGTGTTAATCT 25 ATAAAATGACATCCAAGTGGATGATGATTTTTTTTGCATGTCCCCCTGCTTAGATT TTTTTAAAATATATAGTCAAAAATTAACATCCTTCTTTAAAAATACAGAAGGGAAA ATTCGANCTCGGNCGACTTGGCCAATTCGCCCTATAGNGAGTCGNATTACAATTCA CTGGGCCGNCGNTTTACAACGTCGNGACTGGGAAAACCCTGGCGTTACCCNNCTNA 30 TCGNCTTGNAACAATNCCCNTTTNGCCAGNGGGG

#### Sequence ID 1255

10

# Sequence 1256

TTGTGTTGGTACCCGGGAATTCGCGGCCGCGTCGACGGAGTTTTACCTTATTACAC 15 TTTAATCTCTGGATTTACCCCATCTCATTTCTCTTTTAGGAAAACTGTTTGTATGT GGTGGCTTTGATGGTTCTCATGCCATCAGTTGTGTGGAAATGTATGATCCAACTAG AAATGAATGGAAGATGATGGGAAATATGACTTCACCAAGGAGCAATGCTGGGATTG CAACTGTAGGGAACACCATTTATGCAGTGGGAGGATTCGATGGCAATGAATTTCTG AATACGGTGGAAGTCTATAACCTTGAGTCAAATGAATGGAGCCCCTATACAAAGAT 20 - ${\tt TTTCCAGTTTTAACAAATTTAAGACCCTCTCAAACTAACAGGCTTAGTGATGTAAT}$ TAACAGCAACACAAAGCTTTTGCATATTGCATACTATTAAACATGCTGTACATACT TTTTGGGTTTATTTGGAAAGGAATGCAAAGATGAAGGTCTGTTTTGTGTACTTTTA 25 TCATTTCAAGAAGTCCCCTCTCCTCCACATTTGTTTTTGCCAATTTGCACATTAAAT GACTCTTCCCTCAAATGTGTACTATGGGGTAAAAAGGGGTAGGGNTTAAANATGTAA ACAGTTGGGTTTTTTAAGGGNCCTTTTTCATAACTGGAACACTCTNTACAAGGNTN  ${\tt CTTNTTAAATAACTTGACTTTTTTTTTTTTNTAAANGNANCTTCNTGCTTCCA}$ TAAAAAAAAATTTAANTNGNCANCTNTGCTGCGCGCCANTTNGCTNGNCCNT 30 GGCATTCCCTAGGGANGNTNAATANTGGCNNNTTAACNNGGCNGNAACNNNNNCCA NT

#### Sequence ID 1331

GGGCGATGCATGCTTTATTAAGGCTCTTGTTTCACCTGGCAGTGTACTGTATCAAC
GTATAATACAGAAAAAAAATCTCTTTAAGGTCCTCCTTCACAAAGACATAGAGTGA
AACTCCCTTTACATGTCAGTATTTGTTCAACACTTTAGGCAACTTGACTGTCAGTG

10

30

TTAAAATGGAAAACAGGAAAATGGAAAAATCTGACCAATTCTGCCACCTTGAGACT TTCATATAGACCTTGCACAACAATTGTATAGATCACACCCGGCTGTATTTAATAT GTAACATTTTCACACATATTAAAGATACAGAAGTATTAAAAAACCCCCAATGTTAA TGTATTTGCTTAAAAGGCACAAGTTTCACATATCTGTCTAGCTATCTGTTGGTAAT ATAAATA'TTTTTTTAAGGAGAAACTAGAATGTTTAGCTAGAAAATTCCACAGCCT GTGAAGAAATATTTCAAAATGGCCATAAAGGAGGTAAAAATGAAAACCATAACCTA AATCTGTTCCGGGCTGTCTGTCCATCAAATGGGCAGGTCTGGGAATGAGGC ACCTTCGGCCGTTCAGAAGTGGCCTGAACAGAATGCTGGAACCCAGGCTGGACTCG GAC

## Sequence ID 1332

15 TGTGTGTCTTAATTGAATAATAGTAGATTTATAGATTAAAGATCTATGGGTTTTTA ATATGGATTAGAAATCTGTGGGTTTTTGATATGGATTAGAAATCTGTGGGTTTTTA ATATGGATTGGAAATCTGTGGGTTTTTAATATGGATTAAAAAACATCTGTGGGTTT TTAATATGGATTAAACATCTGTGGGTTTTTAATATGGATTAAACATCTGGGTTTTT 20 AATATGGATTAAACATCTGTGGGTTTTTAATATGGGTTAAAAATCAAAAGAAAATG AACTATTTGCTCCAGTGCAGGAAAATACAGGCAATACTGGATACAATTAGATGGTC AGGAGCGATAACCCGGTTGCCATTGTTTGAAGAAGAAGAATAAGGTGCTAGCATTCC AAGGCTAAATGAACTATTATATGCAGTTATCGTAGAAGAGTACTCAAAAAAATCTG TAAAAAATAAAGAAAGGCCGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTG 25 GGAGGCCGAGGCGGGTGGATCATGAGGTCAGGAGATCGAGACCATCCTGGCTACCA NGGTGAAACCCCCGTCT

#### Sequence ID 1335

CAAGACTCCATCTCAAAAAAAAAAAAAAATCTACAGTGCTGAGTATATAAAATTAT TAACACATTTCACAACAATATGTGTTTGTGGAGTTAAATATTTTTTGTCTTTAAAA CAGGTAATTTTAGTGCATACTTAATTTGATGATTAAATATGGTAGAATTAAGCATT TTAAATGTTAATGTTTGTTACATTGTTCAAGAAATAAGTAGAAATATATTCCTTTG TTTTTTATTTAAATTTTTGTTCCTCTGTAAACTAAAAGAACACGAAGTAATTGGTC 35 ACAATTACTGGTGTTTAACTGCCAAATATGGGTAAATAAGGGAAAATTTTGTTTAA TATTTAGTCCTTCTGAGATGGCTTGAATATTTGAATTTTGTTGTACGTCTATACTG GGTAGTCACAAGTCTTATAAACACTTTAGAGGAAAGATGGATTTCAGTCTGTATTT

15

TTAAACATCATTTATTTTAAATCTGGTGCTGAAAAATAAGAAAAAAATTAAACTGC ATTCTGCTGTTCTTTAGAAGCATTCCTGCGTAAATACTGCTGTAATACTGTCA TTCCTAGAAATGTTTGTCCTTCCCCCACCTGTTGATCCAGGTTAAGGAATACTTTT TTACACTTTATTCAAA

Sequence ID 1336

 $\tt CTTTTCCTCCCGCTGTCCCCCACGGAGGGGACTGCTCTCCCCCGCTGCATCCTTTC$ TGTGAGGTACCTTACCCACCTCAGCACCTGAGAGGGTGAAATAGAATTCTAACCTC  ${\tt GACATTCGGGAAGTGTTTTTGAGAAGTCTCGGTCGGTAAGGGAAGTCTTCCAAGTC}$ 10 CGTGCAGCACTAACGTATTGGCACCTGCCTCTTTCGGCCACCCCCAGATGAGG  ${\tt CAGCTGTGACTGTGACGAAGGGAAGCCACGACTCTGACCATAGTCTTCTCAGCTT}$ CCACTGCCGTCTCCACAGGAAACCCAGAAGTTCTGTGAACAAGTCCATGCTGCCAT CAAGGCATTTATTGCAGTGTACTATTTGCTTCCAAAGGATCAGGCCCTGAGAACAA TGACCTTATTTCCTACAACAGTGTCTGGGTTGCGTGCCAGCAGATGCCTCAGATAC CAAGAGATAACAAAGCTGCAGCTCTTTTGATGCTGACCAAGAATGTGGATTTTGTG AAGGATGCACATGAAGAAATGGAGCAGGCTGTGGAAGAATGTGACCCTTACTCTGG CCTCTTGAATGATACTGAGGAGAACAACTCTGACAACCACAATCATGAGGATGATG TGTTGGGGTTTCCCAGCAATCAGGACTTGTATTGGTCAGAGGACGATCAAGAGCTC 20 -

Sequence ID 1337

CAAGAACTCTGGGACATTTGCAAAGGGTATGGCATATGTGTAATGGGAATACCAGA GGAGAGGAAAGACAGGAAGTCAAAAAAAGAATTTTTCCAAATTAATGATAGGTTCC CTTAAGCATATCATACTTAACCTGCAGAAAATTACAGACAAAGAAAAAACACCAGA GGGGAAGCTGGCAGAAACATACCACCTATAGCGGAAGAAGAATAAGAATTACATCA GACTTCCCTTCAGAAATCTTGCAAACAAAAAGATGTAGCACAATATTTAAAGTATT AAAGGAGGCCGGGCCGGTGGCTCGGGCCTGTAATCCTAACACTTTGGGAGGCTGA GGCAGGAGGACCATGAGGTCAGGAGATCGAGACCATCCTGGTGATGGTGATACCCC ATCTCTACTAAAAATACAAAAAATTAACCGGGCATGGTGACACGCACCTGTAATCC CAGCTACTTGGGAGGCTGAAGCAGGAGAATCGTTTGAGCCCAGGAGGTGGAGGTTG CAGTGAGCCGAGATCACTGCACGCCTGGGCAACAGAGCGAGACTCCATCTC AAAAA

35

30

Sequence ID 1338  WO 2004/046382 PCT/GB2003/005102

- 261 -

15

20

25

35

10

5

Sequence ID 1344

30 Sequence ID 1348

10

# Sequence ID 1351

 ${\tt TTTTTTTTTTTAAAAGAGATGGGTTCTCACTATGTTGCCCATAATGTTTATGAG}$ ATTAAGTTCATCTTTTTTATCTGAGTAGTATTTTATTGTATGAATATACCACCATT 15 TATTTATCTGTTGGTTATTTCCAGTTTTGGGCTATAATCCAAAATGCTTTTTTCAA ACAATAGGCTATATATCATTAATGTCCGTTTATCAGCAGTATAAAATATCTTACCA TAAATATTAATAAAAGAAGCATTCATATATAAAATATAGATATTTCAAACCCTACA GAGGGCCTTTTAATGATTAAATATTTTGTCCTTACAAAAAGGTCCAGGTAATTACA  ${\tt CCCATGAGGTTAACCTGCCTTAGTGCAGGACTTAAAATAAGGCTTCTCCTGCCATC}$ 20  ${\tt TCTCTCCATTTGTAGAATGTGAAATTCTTTAAAATGCATCCTATATTAGGAATACT}$ ATAGCTGTGCACTGGTGTTTGTTCTCTTTTTAAACTCGGGACCGTATATATCTGC TCAAATTGCCCAAGTATACATATGCTGCACTCCATCAAGTGTCAGGCCACATTCTA TCAGCACAGCGTGACTGCCTATCAGTGACAATATAAGTGAGCTCTATTTGGATCCC  ${\tt TCTTACCCTACCTTTTATATTTATGACAGCATTATCATAAAACTCCAATATTCTTC}$ 25 AATAACTTACATGTTTGTTGTAGGATAAAATTATTACCCTCAATGAACTACAT

#### Sequence ID 1352

ACCAGCTTCTTCACAGGTTCCACGAGTCATGTCAACACAGCGTGTTGCTAACACAT

CAACACAGACAATGGGTCCACGTCCTGCAGCTGCAGCCGCTGCAGCTACTCCTGCT

GTCCGCACCGTTCCACAGTATAAATATGCTGCAGGAGTTCGCAATCCTCAGCAACA

TCTTAATGCACAGCCACAAGTTACAATGCAACAGCCTGCTGTTCATGTACAAGGTC

AGGAACCTTTGACTGCTTCCATGTTGGCATCTGCCCCTCCTCAAGAGCAAAAAGCAA

ATGTTGGGTGAACGGCTGTTTCCTCTTATTCAAGCCATGCACCCTACTCTTGCTGG

35

TAAAATCACTGGCATGTTGTTGGAGATTGATAATTCAGAACTTCTTCATATGCTCG

AGTCTCCAGAGTCACTCCGTTCTAAGGTTGATGAAGCTGTACCTACAAGCC

CACCAAGCTAAAGAGGCTGCCCAGAAAGCAGTTAACAGTGCCACCGGTGTTCCAAC

TGTTTAAAATTGATCAGGGACCATGAAAAGAAACTTGTGCTTCACCGAAGAAAAAT ATCTAAACATCGAAAAACTTAAATATTATGGAAAAAAAACATTGCAAAATATAAAA TAAATAAAAAAGGAAAGGAAACTTTGAACCTTATGTACCGAGCAAATGCCAGGTC TAGCAAACATAATGCTAGTCCTAGATTACTTATTGATTTAAAA

5

10

15

Sequence ID 1353

ACATTCTGGAAAAGGCAAAAGGGAGGAAGAACTGATTAGTGGTTAGCCCAGGGTTA GAGTTGGGGAGAGATATAATGAGGGAACTTTTGTGGATTCTGTACCATGATTATG ATTACACAAACCTATGCATACATTGAAACACATAGAACTATACGTTGAAAAAAGTG CTTAACACATTATCATCTATGTCAGTTTAACAGTTAGTAGACTTAGGCCAGGTGTC ATGGCTCACTCCTGTAATCCCAGTGCTTTGGGAGTCTGAGGTGGGACGATCTCTTG AGACTAGGAGGGGGTTTGAGACAAACCTAGGCAATGTAATGAGACTCTTTCTCTAC GGGAGGCTGAGGTGGGAGGATTCCTTGAGCCCAGAAGTTCAAGGCTACAGTGTGCT ATGATAGAGCCACTGCACCCTGGGCAACCAGGTGAGACCTTGTCTCTAAAA TGAATAAATAAAT

Sequence ID 1355

- 20 TGGTCTTTCACCCAGCCAGGGAGAAGGTTCTTCGCTCAGTATGAAGAAAAGCAACC GAAGTAAAGATTTAGAATTCACCTAAGTCCAAAGGAAAACACGTGGTTTTTAAAGC CATTAGGTAAAAAAGTTCTCAATAAAGGCATTACAATTTTTTAGGTTTAGAAAGA 25 AGAAAATGCAAGTTACTTTTTTTGGAAATAATACTCACTGATTATGGATAAAATGG AATATTTCAGATACTATATTGGCTGTTTCAAAATAGTACTATTCTTTAAACTTGT AATTTTTGCTAAGTTATTTGTCTTTGTTGTATAAATATGTAAAAAATATTTA
- 30 Sequence ID 1359 CGGGATCCCTAGTATAACACATTCAGTGTTCCCCTTTCAGTCTTACTACTTTGACC GCGATGATGTGGCTTTGAAGAACTTTGCCAAATACTTTCTTCACCAATCTCATGAG GAGAGGGAACATGCTGAGAAACTGATGAAGCTGCAGAACCAACGAGGTGGCCGAAT CTTCCTTCAGGATATCAAGAAACCAGACTGTGATGACTGGGAGAGCGGGCTGAATG 35 CAATGGAGTGTGCATTACATTTGGAAAAAATGTGAATCAGTCACTACTGGAACTGC ACAAACTGGCCACTGACAAAATGACCCCCATGTGAGTATTGGAACCCCAGGAAAT AAATGGAGGAAATCATTTGCCTTAGGGATTGGGAAAGCTGCCCACTAACTGTCTTC

CCCATTGTTTTGCAGTTGTGTGACTTCATTGAGACACATTACCTGAATGAGCAGGT GAAAGCCATCAAAGAATTGGGTGACCACGTGACCAACTTGCGCAAGATGGGAGCGC CCGAATCTGGCTTGGCGGAATATCTCTTTTGACAAGCACACCCTGGGAGACAGTGAT AATGAAAGCTAAGCCTCGGGCTAATTTCCCCCATAGCCGTGGGGTGACTTCCCTGGT CACCAAGGCAGTGCATGCATGTTGGGGTTTCCTTTACCTTTTCTATAAGTTGTACC AAAACATCCACTTAAGTTCTTTGATTTGTACCATTCCTTCAAATAAAGAAATTTGG

# Sequence ID 1360

10

15

5

20 -

25

30

35

# Sequence ID 1361

Sequence ID 1364

10

15

35

5

Sequence ID 1365

CACCAGGCTGTCTTCAGATACTTCATACAGAAATGAGCCTCCCTGTGGGGTCCTCT
TCCCTCCTTCAGCCTGTCCATCAACACAGCATTGCGGGATCCTTACCATGGCATCC
AGCCCTGGAGATGCTTCAGGAAAGTTGCAGGTCCATGCTGCAGGACAGGCTCAGAT
CAGCAGAGACGCATCTCACATCGGGCTGTGAAATTCAAGTTGAGCTGCAATTGGCA
ATGAGAA

Sequence ID 1366

GTTATTCACTGAGACCGTGCCCCGGTTATGAGGTTGTACCAGAAAGCAAGTATTCA 20 CCTTTGCTTTGAGGGCAGGTCTTTCCCCAAAATGCAGACACGAAGGTGCAAAGTGA AGCTGCCAGTCTTGCAAAAGATGTAACTTGTCACGAAGGCCACGAGTGGCAGGGAG GAGATGAGACAATCATAAGGGGAGATATCAGAGAAAATCGTAAGGGGAGCAGATGG TTGTCAAGAGAATAGGCTGACCATCGAAGGACTGGCAGAAGCTTTCAGAAAACCAC 25 TGGACGCTGGGCACAGTGGCTTAGGCCTGTAATCCCAGCACTTTGGGAGGCTGAC GCAGGTGAATCACTTGAGGTCAGGAGTTCCAGACCAGCCTGGCCAACATGGTGAAA CCCCATCTCTACAGAAAATATAAAAATTAGCCAGGCGTGGTGGCACAAGCCTAGAA TCCCAGCTACTTGGGAGGCTGAGGCAGGCGAATGGCTTGAACCCAGGAGTCAGAGG CTGCAGTGAGTCGAGATTGTTCCACTGCACTCCAGCCTGGGTGACAGTGCAAGACT 30 CCTTCCAAAAAAAAA

Sequence ID 1367

# Sequence ID 1368

- Sequence ID 1370

  CGAAAGGACTACAGAGCCCCGAATTAATACCAATAGAAGGGCAATGCTTTTAGATT

  AAAATGAAGGTGACTTAAACAGCTTAAAGTTTAAAAGTTGTAGGTGATTAA

#### Sequence ID 1371

GTCCAGNAGAAAGTTCAGTGACTTGTCCAGAGCTGCAGGTCTTAAGAGGCTGAAAT 10 CTCGCCTCTGCCTCGAGGCTGCGGTTCCACTGACCCATACTACTTGCCTTCAGGAA AGAGAAATGGTGTAGGAAGGCTGTGGATGAAGACGCTTACATTCATGAAGGATTTG GATAGGCGAACATGAGCTTTTCCACCAAATTTCAGAATTTTAAGAAATGCCTTAAA TTATTTCTTAAAAATCAATTTGGGGCAGACGAGAAGTTCTGATAATAGTTTTTAGG GAACATGATAAAATTCTGACCTTAGAAGTGGTATACCAGTTTGAGAAGAAGAACAA. 15 ACCAGAATGACTTAAGAGTGTTACTCTTCTTTTTCTGAGAGAACAATAGCATCATC TCAGAAAGCCTTTCATGCCATTAATAGGTAAGAATCTGGGCTTCTTGGACCATGGG TTAGACTTTCTTACAAAACCATAATATGCATTTCCTAGCAAAATTTATGCTATTAC ATTTCCTTATCTCAACAAGACTGGTAAATTCAGTACTTATTCCTCAATTTTCCTA 20 . GTTGTCAACTTACTTTCAGGATGGACTTTTCTTTTTGTGAGTTTGTGACCTAAATAC AATAGTTGTTATGCATGTCCAGTTTATGGAAGTACCACTGCAATANCAG

# 25 Sequence ID 1372

30

35

- 268 -

Sequence ID 1374

GCCTGTAATCCAAGCTACTCGGGAGGCTGAGGCAGGA

Sequence ID 1380

CCAAACCCAACTGGTCCAGTAGGATACTCACCTTACAGGGGGCGTCTCAAGAGTCT  ${\tt CACAGTTCCCTTGGGTCTTAAGAGACTCACTGTTGGACCAGGCGTGGTGACTCACG}$ 10 CCTGTAAAACCAGCACTTTGGGAGGCCGAGGCGGGCGGATCAGTTGAGGTCAAGAG TTCAAGACCAGCCTGACCAAGGTGCTGAAAACCCCCGTCTCTACTAAAAATACAAAAA TTAGCCAGGCATGGTGTGTGCGCCTGTAATCCCAGCTACTCCAGAGGCTGAGGCA GGAGAATCTCTTGAACCCAGGAGGTGGAGGTTGCAGTGAGTCGAGATCATGCCACT 15 AAAAGAACCTCACAGTTCAGCAGGGTTCTAGCATGAGACAATGAGGACAAGGGTAG GTGAGCAGGTGGAAAGAGTGAGAACAGGTCAATTGTGATGGAGAAAATAATAAAGA CAGAAAAGGCAGAAGACTGCCTGGCAGAAGACCTGTCCCAGCAGATACAAAAATAC AGACAACAGGAGCCAGCATAGACCCTTGACCTGTGTAAGTCTTTCTCAGGCCTTCT 20 TTTAAGTAGAAACATGCCTTTGAAAAAAAGTTTTAATAAACAGGAAAATCATAAAT CCCTATTTACATAAATAATATCCTGGTCTTATTCTTAAAACCATTGATTTTTCA CGGCTCATTAANAAAGCTGGGCGAGGTGGCTCACGCCCGTCATCCTAGCACTTTGG GAGGCCGAGGCGGCANATCACAAGGTGAGGAGTTGGGAGACCAGCCTGACCAACA CGGTGAAACCCAGTCTCTACTAAAAATACAAAAATTANCTGGGGGGTGGTGTGT

# Sequence ID 1382

25

30

35

10

30

35

CTAGCATGGGATTTTGTAAGAGAAAATTGGACCCATCTTCTGAAAAAATTTGACTT
GGGCTCATATGACATAAGGATGATCATCTCTGGCACAACAGCTCACTTTTCTTCCA
AGGATAAGTTGCAAGAGGTGAAACTATTTTTTTGAATCTCTTGAGGCTCAAGGATCA
CATCTGGATATTTTTCAAACTGTTCTGGAAACGATAACCAAAAATATAAAATGGCT
GGAGAAGAATCTTCCGACTCTGAGGACTTGGCTAATGGTTAATACTTAAATGGTCA
ATAGAAAAAAGTAGGCTGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGA

Sequence ID 1387

Sequence ID 1389

15 GNTTTTCGGAAACGGAGTCTCGCTTTCTCGCCCACTCTGGAGTGGNGCAGTGGGGN GGTCTCAGCTCACCACGCCTCCACCTCCTGGGCCCAAGCGATCCTNTCACCTCAG CCTCCTGCGTAGCTGGGACTACAGGCGTGCACCACCATTCCCAGGTAATTTTTGTA TTTTTTGTANANACAGGGTTTCACTGTTGTTGCCCAGGCTGGTCTCGAACTCCTGC TTCAGTCTGCCANAATGCTGGATTCTAGGCGTGAGCCACCGNGCCTGGCCCAAAAG 20 TTACTTTCTTACAGAAGCAAAGCTTTAATGCATTTTACTGAATGCTTATAGCTTT GTAGATACTGAAAAGAGTATGAGCGTCACATACAGACACATNTAACAGCACTGCCT CCAACCAGCCCTACCCACTGGTCAGGNGAGTAANAATCAAAATTCTTTTCTGNGA GTGGAACGGAAATTTCATCTCTCCTCCTCAGGCAAGTAGTTAANAGGCTGGNGGGA GTCATGGCCCCATTTTGTTCAAAATACAAGCTCCACAGGAACAAAAGGCTGAACTG 25 CTCACCTCCCAACTGATGAACCTCGTCTTTGTTCCATGTCAAAGGGGCCTTTGTGT TACTGCAGCAGAAACTCCAGCTATCAAACCATCAGGCACCAAAAGTAAAACTCCTT TCTCTAAAAAGACCTCTCTTTACCTGAGCCTTTCAATGCATCTTTGCCCCCANATA ATCCTGGATGAGATAATCCCCAGAGGAANACCAGCGCTTGCCTAGTGAAATTATAC TATGAGACAAGGGTAAAAGACCTCAAANACCGGGTTGGCAGGTAAGGGAGTAGGGN

Sequence ID 1390

- 270 -

#### CTTAGGAGAGGAGT

Sequence ID 1391

CGGCTNCTACCCTGCGGAGATCACACTGACCTGGCAGTGGGATGGGGAGGACCAAA CTCAGGACACCGAGCTTGTGGAGACCAGGCCAGCAGGAGATGGAACCTTCCAGAAG 5 TGGGCAGCTGTGGTGCCTTCTGGAGAAGAGCAGAGATACACGTGCCATGTTCA GCACGAGGGGCTGCCGGAGCCCCTCACCCTGAGATGGAAGCCGTCTTCCCAGCCCA CCATCCCCATCGTGGCCATCGTTGCTGCCTGGCTGTCCTAGCTGTC CTAGGAGCTATGGTGGTGTGTGTGTGTGGGAGGAGGGCTCAGGTGGAAAAGG - AGGGAGCTGCTCTCAGGCTGCGTCCAGCAACAGTGCCCAGGGCTCTGATGAGTCTC 10 TCATCGCTTGTAAAGCCTGAGACAGCTGCCTGTGTGGGACTGAGATGCAGGATTTC TTCACACCTCTCCTTTGTGACTTCAAGAGCCTCTGGCATCTCTTTCTGCAAAGGCA TCTGAATGTGTCTGCGTTCCTGTTAGCATAATGTGAGGAGGTGGAGAGACAGCCCA 15 ATCTTTCCTGTTCCAGAGAAGTGGGCTGGATGTCTCCATCTCTGTCTCAACTTCAT GGTGCGCTGAGCTGCAACTTCTTACTTCCCTAATGAAGTTAAGAACCTGAATATAA TTCCTGGAAGTTGAGAGAGCAAATAAAGACCTGAGAACCTTCCANAATCCG

Sequence ID 1395

15 Sequence ID 1396

5

10

20

25

30

CAAACACTATGTTATTTTATGAANAAGACTTGAACATCTATGGATTTTGGTATTTG CAAGGGGTGAATGGGGTATTTGCAAGCAGTGAATGAGGAGGCCTGGAACCAATCTT CTGCTGATATTGAGGCACAACTGAAAAAGGTATATTACTTAAATCTCTTATTGTAT TGTAAACTGTATAAGTAATGAAATTAAAAGGCAGAAATTGTCAGACTGAATAAAAT GAAAAGACCAAACAATATGCTGCTTACAAGAAACACAATTCAAATATAAGGACACA ATTAGTTTAAAGGAAAAGAACTGGAAAAGATATACCATGATAACACAAGTCAGAAG AAAGCTGCTGTGGATATATTAATATGAGATGTAGATTTCAGAGCAGTGAATATTGC CAGGCATAAAGAAAGTTATTACATAATAATTAAGGTATCAGTTCATCAAGAAGATG TAATAACCCTAAGTATTTATACAACTAATATCAGAGCTTCAAAATACATGAAGCAA AAACCAGTGGAATTGATAGGAGAAACACACAATTACACAATTATAGTCAGAATTTT CAACATATCTTTCTCAATGGAGAAAACAACTAGACAGGAAATCATTAAGGATATAG ATGATTAAATTATATGATCAACTACCTGGACGTAATTGGCATTTATGGAACACTG CACCACCAACAGCAGAGTACATATTATTTCAAGTACACAGAAAACAGTTACCAAT ATAGACCATTTTCTGGGTCATAAAACACATCTCAATAAATGTAAAACAATTAATGT TATATAAAGTATGTGCTCTGACCNCAAAGGAATTAGAGATCAATAAAAGAACATCT TTGAAAAATCTCACNTATTTAAAAACTAATAACTCACTTCTAAATAACTCCTGTNT CAAGAGAATNAAANGG

Sequence ID 1397

35

CCCAGCCTCACTGCGCCCGTCAGGCCAGGCAGCTGCCCTCAGGGTCTGCCAAGGT GGGGGTCAAGGGCCATGGGGGCAGGTAGCTCTGCCTGCAAAGCCCACAAGCATGTC

15

20

25

30

35

10

5

Sequence ID 1399

# Sequence ID 1440

TACCACAGTTTCTCTGCATTTTTCCTCTTTGACCACTAACCATGTGAAATTCTC
ATATTGACCTTTATAATGATCATGAACTCTTAGTATCATTGGGAAGGCCACATTTG
CCACTTATGATTGTAAACCTTATCCTCCATTTTTCCTGTTATTGTTGGTGCAAAAA
GCACCTATTATACCAGGACTTTAAAAAATCAGTCTGATAAGTCTTTGATAAGTCTAA
TAATAATAACTGATAAGTCCATTGAATTTGCTTCTGATTACTTTTTCTTTAGTAGC
TAAACATGTATGTACTCCTATGATTACAATGAACACTCCTCCCATTTAAATTAAT
TATTTACATTGATGAAATAGCAAAAATGTTAATGACTAAATACTGTCTTGGTTTTTT
CGTTCCAGGTCAGTCAATATTAACTTCTTATAATTTTCTTTT

Sequence ID 1448

TCATAAGGAAAGGT

GGCCACCGGGTGCAAGGTCAGGGCTGGGGTGGAGGCTGGGAAGCCCAGGGCTTGGC
CCACTGTGGCCGCCTTGTGTGTGTCACTGCTTTCCTGGGCCTGCTGTGAGCTCCCTC
TAGGACCCCAGGCCTGTCTGGTGGGTCACTGTGACCACCACCTTGCACAGCACCTG
GCGCGTGGCAGGTGCTCAAACATTACTTGTTTCGGAATGAACTTCATCTTGCTCTT
GGCTTTTTGACTAATGCTGTGGAACATCTGACTAATTAGTGACTCTTTGGGGCCCC
CAGTTTCCCAGCTATAAAGTGGTAATATTAAGATAATATTCGGCCGGGCGCGGTG
GCTCACGCCTGTAATCCCAGCAGCACTTTGGGAGGCCGAGGTGGGCAGATCACGAG
GTCAGAAGATCGAGACCATCCTGGCTAACACGGTGAAACCCCATCTCTACTAAAAA
TACAAAAAATTANCCGGGCGTGGTGGCCGGGCGCCCTGTAGTCCCAGCTACTCANGAG
GCTGANGCAGGAGAATGGTGTGAACCCGGGAGGCAGAGTTGCAGTGAACCAAAAAT

30

35

AATCAGGGCCGCAGTGTGTTCTGCGCCTGCCCAGAGCTGACTCCTGATTTAACCGC
TGGCGTAACCGCGGGTTGCACGCATGCGTGCTGAAAAGCCTTTCACCCTCACGTGG
TTTCTTTTTTAACCAGTCATCAAGCGAGGCTCGCGCGCAGGCCCCGCGTTGGAAAA
TGGCGGGGAAGCTGAAACCTCTGAATGTGGAGGCGCCAGAAGCTGCTGAGGAGGCT
GAAGGTAGTGAGGGCAAGTGGGCTGCACTCCTTTCTCTCCAACCAGGGCAGAAAGG
AGGGAGGATTCGTCCCATTACAATAATGAAATAATGATATTCTAATTTTTTAAAT
AAAATGTTAAGCCTTTTGTTATTGAA

## Sequence ID 1450

10 CGTCCCTACAGCGGGCCTGCCGCCTGCTGGGCCGTCTGCGCTCTGCACCTTGGC  $\tt GTCACCCTCGTTTACTACCTGGCTGGCCGCCGACCTGAGCCGCCTGCCCCAACTGGT$ CGGAGTCTCCACACCGCTGCAGGGCGGCTCGAACAGTGCCGCCGCCATCGGGCAGT CCTCCGGGGGGCCCGGCCGCCTCCTNTAGGCGCCTCC TCCCAGCCGCGCCCGGGTGGCGACTCCAGCCCAGTCGTGGATTCTGGCCCTGGCCC 15 CGCTAGCAACTTGACCTCGGTCCCAGTGCCCCACACCACCGCACTGTCGCTGCCCG CCTGCCCTGAGGAGTCCCCGCTGCTTGGTAAGGACTCGGGTCGGCGCCAGTCGGAG GATTGGGACCCCCCGGATTTCCCCGACAGGGTCCCCCANACATTCCCTCAGGCTG GCTCTTCTACGACAGCCAGCCTCCCTCTTCTGGATCAGAGTTTTAAATCCCANACA  ${\tt GAGGCTTGGGATGGGAGAGAGGTTTGCGAGGTGGGTCCTTGGGGAGTCCT}$ 20 GTTGGAGGCGTGGGGCCGGGACCGCACAGGGAAGTCCCGAGGCCCCTCTAGCCCCA  ${\tt AAACCANAGAAGGCCTTGGAGACTTCCCTGCTGTGGCCCGAGGCTNAGGAAGTTTT}$ GGAGTTTTGGGTCTGCTTANGGCTTCNAGCAGCCTTGCACTGAGAACTTTGGTAGG GACCTCGAGTAATCCACTCCNTTTTNGGGACTGACGTGAGGCTCCCGGTGGGGAAA 25 GANACTGACCTNTC

# Sequence ID 1453

20

25

30

35

GCAGGTTGCTCCACAGGTAGCTCTAGGAGGGGCTGGCAACTTAGAGGTGGGGAGCAG
AGAATTCTCTTATCCAACATCAACATCTTGGTCAGATTTGAACTCTTCTAT
GCACTCAAAGCTTGTTAAGATAGTTAAGCGTGCATAAGTTAACTTCCAATTTACAT
ACTCTGCTTAGAATTTGGGGGAAAATTTAGAAAATATAATTGACAGGATTATTGGAA
ATTTGTTATAATGAATGAAACATTTTTGTCATATAAGATTCATATTTACTTCTTAT
ACA

Sequence ID 1454

Sequence ID 1456

Sequence ID 1460
CCACAACTGTGTTCACTAGCAACCTCAAACAGACACCATGGTGCACCTGACTCCTG

10

15

20

25

30

35

AGGAGAAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTGGT
GGTGAGGCCCTGGGCAGGCTGCTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGA
GTCCTTTGGGGATCTGTCCACTCCTGATGCTGTTATGGGCAACCCTAAGGTGAAGG
CTCATGGCAAGAAAGTGCTCGGTGCCTTTAGTGATGGCCTGGCTCACCTGGACAAC
CTCAAGGGCACCTTTGCCACACTGAGTGAGCTGCACTGTGACAAGCTGCACGTGGA
TCCTGAGAACTTCAGGCTCCTGGGCAACGTGCTGTCTGTGTGCTGGCCCATCACT
TTGGCAAAGAATTCACCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGTGGCTGGT
GTGGCTAATGCCCTGGCCCACAAGTATCACTAAGCTCGCTTTCTTGCTGTCCAATT
TCTATTAAAGGTTCCTTTGTTCCCTAAGTCCAACTACTAAACTGGGGGATATTATG
AAGGGCCTTGAGCATCTGGATTCTCCCTAATAAAAAAACATTTTTTCATTG

Sequence ID 1490

ATGGGCATCTCTCGGGACAACTGGCACAAGCGCCGCAAAACCGGGGGCAAGAAA
GCCCTACCACAAGAAGCGGAAGTATGAGTTGGGGCGCCCAGCTGCCAACACCAAGA
TTGGCCCCCGCCGCATCCACACAGTCCGTGTGCGGGGAGGTAACAAGAAATACCGT
GCCCTGAGGTTGGACGTGGGGAATTTCTCCTGGGGCTCANAGTGTTGTACTCGTAA
AACAAGGATCATCGATGTTGTCTACAATGCATCTAATAACGAGCTGGTTCGTACCA
AGACCCTGGTGAAGAATTGCATCGTGCTCATCGACAGCACACCGTACCGACAGTGG
TACGAGTCCCACTATGCGCTGCCCCTGGGCCGCAAGAAGGGAGCCAAGCTGACTCC
TGAGGAAGAAGAGATTTTAAACAAAAAACGATCTAAAAAAATTCAGAAGAAATATG
ATGAAAGGAAAAAAGAATCAGCAGTCTCCTGGAGGAGCAGCTGCCAG
GGCAAGCTTCTTGCGTGCATCGCTTCAAGGCCGGGACAGTTGCCGCAG
CTATGTGCTAGAGGCCAAAATCAGCAGTTCTATCTTAGGAAAAATCAAGGCCCGCA
AAGGCAAATAAATCCTTGTTTTGTCTTCACCCCATGTAATAAAAATCAAGGCCCGCA
AAGGCAAATAAATCCTTGTTTTTGTCTTCACCCCATGTAATAAAGGTGTTTTATTGTTT

#### Sequence ID 1491

WO 2004/046382 PCT/GB2003/005102

- 277 -

TAGTTTTAGTTATAGTTTTAGTTGTAGTACAAAAAAGCATTTTCTGTAAGCTTAAT
TTCTTTCCCCCTTCCCGCTTTCCCAGTCAGATGACTTTAGTGATTTTGGAGTTGTGTG
CTTTATAAGTGCATTCCTCAGAGGACTTAATATTACTAAGATTTTAGCAACNCTGA
AATATGTT

5

10

15

TCCTTAACCAAAACTGCCAAGAAAGGCTTGGAATTGAAACAAAACCTGATANAANA

Sequence ID 1493

GGTAAGAGGTTGTTCTTTT

- 20 TGTNTCAAAAAAAAAAAAAAAGAACGGNAATGTACTGGAGATGTATTTGATAACCAA GGNTTTAGGTAAATTTTCACCAGTATTAGTTNTATTTGCAAAACTGAAAAATGTTGT AGGCTTAATATAAAATAACCACATTAGTGAACATTATATCTCTTAGAAGAAAGGCC ATATTTTGCTCCTGCTTCTGTAAAAATATTATTTGTTTGAAGGGGAAATAATGGTA 25 AAGAAGGAAAATTCTGGAGTTACACTCCACAACCTTGAACATACTGACGGACATCT CTGTTTTGACAACGATTTCTCCATGCCACCCATGCTNTAATGCCTTGTGGATCACG GACAACCCTCTTTGCACAAGCTACAGCATCAGCGATGTTATCTTGCAGCAAAGCAC TGCAGGATAAATGACAGGCATTAACTGCTCCTGGGGTTTTGCCATCATTACACCAG TAGCGGCTATTGATCTGAAATATCCCATAATCAGTGCTTCTGTCTCCAGCATTGTA 30 GTTTGTAGCTCGTGTGTTGTAACCACTCTCCCATTTGGCCAAACACATCCAGTTTG CTAGGCTGATTCCCTGTAGCCATCCATTCCCAATCTTTTCAGAGTTCTGGCCAAC TCACACCTTTCAAAGACCTTGCCCTGGACCGTAACAGAAAGGAGGACAAGCCCCAG AACAATGAGAGCCTTCATGTTGAC

25

30

## Sequence ID 1495

# Sequence ID G6

GGATTTTTGGTCCGCACGCTCCTGCTCCTGACTCACCGCTGTTCGCTCTCGCCGAG
GAACAAGTCGGTCAGGAAGCCCGCGCGCAACAGCCATGGCTTTTAAGGATACCGGA
AAAACACCCGTGGAGCCGGAGGTGGCAATTCACCGAATTCGAATCACCCTAACAAG
CCGCAACGTAAAATCCTTGGAAAAGGTGTGTGCTGACTTGATAAGAGGCGCAAAAG
AAAAGAATCTCAAAGTGAAAGGACCAGTTCGAATGCCTACCAAGACTTTGAGAATC
ACTACAAGAAAAACTCCTTGTGGTGAAGGTTCTAAGACGTGGGATCGTTTCCAGAT
GAGAATTCACAAGCGACTCATTGACTTGCACAGTCCTTCTGAGATTGTTAAGCAGA
TTACTTCCATCAGTATTGAGCCAGGAGTTGAGGTGGAAGTCACCATTGCAGATGCT
TAAGTCAACTATTTTAATAAATTGATGACCAGTTGTTAAAA

Sequence ID - 61 nt: 362
CTTATTGAAAATTTACTAATTCTTACTTTTTAGGTTTTAGGAGAATACTTTTGGA
TAATTGACTAGCCTCACATTATATTGATAGAGGTTCTTGAAAACTTTAATGCCAAT
TCATGTATCTTATGACTAAAATAGATAATCCATTTAGAAAATTTAAGTCATTCTTGC
GTGCTTGATATGTGTCAGCACTATCCAAGTTGCTAGGGGATACAATGGTGAAGTG
AAAATATCAGCTAGGTGCCGGTGGCTCACACCTGTTATCCCAACAGTTTGGGAGG
CCAGGGTGGGAGGATCACTCAAGCACANGCGTTTCACACCAGCCTGGACAACAT

Sequence ID - 490 nt: 382

ACAAGACCCCATCTTTACCAAAAGTTAAG

35

# Claims:

- A set of oligonucleotide probes, wherein said set comprises at least 10 oligonucleotides selected from:
   an oligonucleotide as described in Table 1 or derived from a sequence described in Table 1, or an oligonucleotide with a complementary sequence, or a functionally equivalent oligonucleotide.
- 2. A set of oligonucleotide probes as claimed in claim 1 wherein said oligonucleotide probes are selected from: an oligonucleotide as described in Table 2 or derived from a sequence described in Table 2, or an oligonucleotide with a complementary sequence, or a functionally equivalent oligonucleotide.
- 3. A set of oligonucleotide probes as claimed in claim 1 wherein said oligonucleotide probes are selected from: an oligonucleotide as described in Table 4 or derived from a sequence described in Table 4, or an oligonucleotide with a complementary sequence, or a functionally equivalent oligonucleotide.
- 4. A set of oligonucleotide probes as claimed in any one of claims 1 to 3, wherein each probe in said set binds to a different transcript.
  - 5. A set as claimed in any one of claims 1 to 4 consisting of from 10 to 500 oligonucleotide probes.
  - 6. An oligonucleotide probe wherein said probe is selected from the oligonucleotides listed in Table 1, or derived from a sequence described in Table 1, or a complementary sequence thereof.
  - 7. A set of oligonucleotide probes as claimed in any one of claims 1 to 5, or an oligonucleotide probe as

WO 2004/046382 PCT/GB2003/005102

#### - 281 -

claimed in claim 6, wherein each of said oligonucleotide probes is from 15 to 200 bases in length.

- 8. A set of oligonucleotide probes as claimed in any one of claims 1 to 5 or 7 or an oligonucleotide probe as claimed in claim 6 or 7, wherein the transcript to which said probe binds is derived from a gene which is constitutively moderately or highly expressed.
- 9. A set of oligonucleotide probes as claimed in any one of claims 1 to 5, 7 or 8 or an oligonucleotide probe as claimed in any one of claims 6 to 8, wherein said probes are immobilized on one or more solid supports.
- 10. A set of oligonucleotide probes or an oligonucleotide probe as claimed in claim 9, wherein said solid support is a sheet, filter, membrane, plate or biochip.
- 20 11. A polypeptide encoded by the mRNA sequence to which an oligonucleotide as defined in claim 6 binds.
  - 12. An antibody to a polypeptide as defined in claim 11.
- 13. A kit comprising a set of oligonucleotide probes immobilized on one or more solid supports as defined in

25

claim 9 or 10.

- 14. A kit as claimed in claim 13 wherein said probes are immobilized on a single solid support and each unique probe is attached to different region of said solid support.
- 35 15. A kit as claimed in claim 13 or 14 further comprising standardizing materials.

- 16. The use of a set of probes as described in any one of claims 1 to 5 or 7 to 10 or a kit as described in any one of claims 13 to 15 to determine the gene expression pattern of a cell which pattern reflects the level of gene expression of genes to which said oligonucleotide probes bind, comprising at least the steps of:
- a) isolating mRNA from said cell, which may optionally be reverse transcribed to cDNA;
- b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotides or a kit as defined in any one of claims 1 to 5, 7 to 10 or 13 to 15; and
  - c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce said pattern.
- 17. A method of preparing a standard gene transcript pattern characteristic of a disease or condition or stage thereof in an organism comprising at least the steps of:
- a) isolating mRNA from the cells of a sample of one
   20 or more organisms having the disease or condition or stage thereof, which may optionally be reverse transcribed to cDNA;
  - b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotides or a kit as defined in any one of claims 1 to 5, 7 to 10 or 13 to 15 specific for said disease or condition or stage thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and
- c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce a characteristic pattern reflecting the level of gene expression of genes to which said oligonucleotides bind, in the sample with the disease, condition or stage thereof.
- 35 18. A method of preparing a test gene transcript pattern comprising at least the steps of:
  - a) isolating mRNA from the cells of a sample of

20 -

25

30

35

said test organism, which may optionally be reverse transcribed to cDNA;

- b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotides or a kit as defined in any one of claims 1 to 5, 7 to 10 or 13 to 15 specific for a disease or condition or stage thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and
- c) assessing the amount of mRNA or cDNA hybridizing to each of said probes to produce said pattern reflecting the level of gene expression of genes to which said oligonucleotides bind, in said test sample.
- 19. A method of diagnosing or identifying or monitoring a disease or condition or stage thereof in an organism, comprising the steps of:
  - a) isolating mRNA from the cells of a sample of said organism, which may optionally be reverse transcribed to cDNA;
  - b) hybridizing the mRNA or cDNA of step (a) to a set of oligonucleotides or a kit as defined in any one of claims 1 to 5, 7 to 10 or 13 to 15 specific for said disease or condition thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation;
  - c) assessing the amount of mRNA or cDNA
    hybridizing to each of said probes to produce
    a characteristic pattern reflecting the level
    of gene expression of genes to which said
    oligonucleotides bind in said sample; and
  - d) comparing said pattern to a standard diagnostic pattern prepared as described in claim 17 using a sample from an organism corresponding to the organism and sample under investigation to determine the degree of correlation indicative of the presence of said

35

disease or condition or a stage thereof in the organism under investigation.

- 20. A method as claimed in any one of claims 17 to 19 wherein said mRNA or cDNA is amplified prior to step b).
  - 21. A method as claimed in any one of claims 17 to 20 wherein the oligonucleotides and/or the mRNA or cDNA are labelled.
- 22. A method as claimed in any one of claims 17 to 21 wherein said probes are as defined in claim 3 and said disease is Alzheimer's disease.
- 23. A method as claimed in any one of claims 17 to 21 wherein said probes are as defined in claim 2 and said disease is breast cancer.
- 24. A method as defined in any one of claims 17 to 23, wherein said set of oligonucleotides as defined in any one of claims 1 to 5, 7 to 10 or 13 to 15 are replaced with a set of oligonucleotides which are randomly selected, preferably from a cDNA library.
- 25. A method of preparing a standard gene transcript pattern characteristic of a disease or condition or stage thereof in an organism comprising at least the steps of:
- a) releasing target polypeptides from a sample of
   one or more organisms having the disease or condition or stage thereof;
  - b) contacting said target polypeptides with one or more binding partners, wherein each binding partner is specific to a marker polypeptide (or a fragment thereof) encoded by the gene to which an oligonucleotide of Table 1 (or derived from a sequence described in Table 1) binds, to allow binding of said binding partners to said

10

target polypeptides, wherein said marker polypeptides are specific for said disease or condition thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and

- c) assessing the target polypeptide binding to said binding partners to produce a characteristic pattern reflecting the level of gene expression of genes which express said marker polypeptides, in the sample with the disease, condition or stage thereof.
- 26. A method of preparing a test gene transcript pattern comprising at least the steps of:
- a) releasing target polypeptides from a sample of said test organism;
- b) contacting said target polypeptides with one or more binding partners, wherein each binding partner is specific to a marker polypeptide (or a fragment thereof) encoded by the gene to which an oligonucleotide of Table 1 (or derived from a sequence described in Table 1) binds, to allow binding of said binding partners to said target polypeptides, wherein said marker polypeptides are specific for said disease or condition thereof in an organism and sample thereof corresponding to the
- c) assessing the target polypeptide binding to said binding partners to produce a characteristic pattern reflecting the level of gene expression of genes which express said marker polypeptides, in said test sample.

organism and sample thereof under investigation; and

- 27. A method of diagnosing or identifying or monitoring a disease or condition or stage thereof in an organism comprising the steps of:
  - a) releasing target polypeptides from a sample of said organism;
- b) contacting said target polypeptides with one or more binding partners, wherein each binding partner is specific to a marker polypeptide (or a fragment thereof)

10

15

35

encoded by the gene to which an oligonucleotide of Table 1 (or derived from a sequence described in Table 1) binds, to allow binding of said binding partners to said target polypeptides, wherein said marker polypeptides are specific for said disease or condition thereof in an organism and sample thereof corresponding to the organism and sample thereof under investigation; and

- c) assessing the target polypeptide binding to said binding partners to produce a characteristic pattern reflecting the level of gene expression of genes which express said marker polypeptides in said sample; and
- d) comparing said pattern to a standard diagnostic pattern prepared as described in claim 25 using a sample from an organism corresponding to the organism and sample under investigation to determine the degree of correlation indicative of the presence of said disease or condition or a stage thereof in the organism under investigation.
- 28. A method as claimed in any one of claims 17 to 27 wherein said pattern is expressed as an array of numbers relating to the expression level associated with each probe.
- 25 29. A method as claimed in any one of claims 17 to 28 wherein said organism is a eukaryotic organism, preferably a mammal.
- 30. A method as claimed in claim 29 wherein said organism is a human.
  - 31. A method as claimed in any one of claims 17 to 30 wherein the data making up said pattern is mathematically projected onto a classification model.
  - 32. A method as claimed in any one of claims 17 to 31 wherein said disease is cancer or a degenerative brain

35

disorder.

- 33. A method as claimed in any one of claims 17 to 32 wherein said sample is tissue, body fluid or body waste.
- 34. A method as claimed in any one of claims 17 to 33 wherein said sample is peripheral blood.
- 35. A method as claimed in any one of claims 17 to 34 wherein the cells in the sample are not disease cells, have not been in contact with such cells and do not originate from the site of the disease or condition.
- 36. A method as claimed in any one of claims 19 to 35 for the diagnosis, identification or monitoring of two or more diseases, conditions or stages thereof in an organism, wherein said pattern produced in step c) is compared to at least two standard diagnostic patterns prepared as described in claim 17 or 25, wherein each standard diagnostic pattern is a pattern generated for a different disease or condition or stage thereof.
- 37. A method of identifying probes useful for diagnosing or identifying or monitoring a disease or condition or stage thereof in an organism, comprising the steps of:
  - a) immobilizing a set of oligonucleotide probes, preferably as described hereinbefore, on a solid support;
- b) isolating mRNA from a sample of a normal organism (normal sample), which may optionally be reverse transcribed to cDNA;
  - c) isolating mRNA from a sample from an organism, corresponding to the sample and organism of step (b), which is known to have said disease or condition or a stage thereof (diseased sample), which may optionally be reverse

transcribed to cDNA;

- d) hybridizing the mRNA or cDNA of steps (b) and
   (c) to said set of immobilized oligonucleotide
   probes of step (a); and
- e) assessing the amount of mRNA or cDNA hybridizing to each of said oligonucleotide probes to determine the level of gene expression of genes to which said oligonucleotide probes bind in said normal and diseased samples to generate a gene expression data set for each sample;
  - f) normalizing and standardizing said data set of step (e);
  - g) constructing a calibration model for classification, preferably using the statistical techniques Partial Least Squares Discriminant Analysis (PLS-DA) and Linear Discriminant Analysis (LDA);
  - h) performing JackKnife analysis and identifying those oligonucleotide probes which are required for classification of said disease and normal samples into their respective groups.

5

10

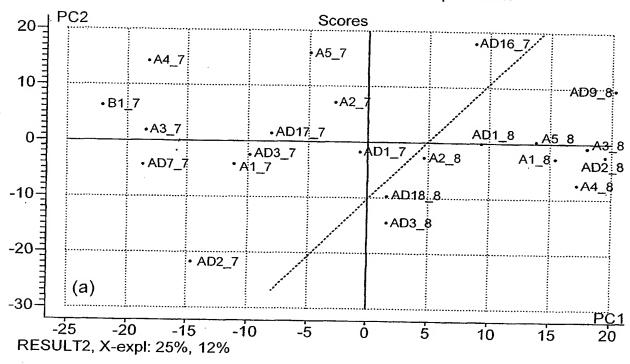
15

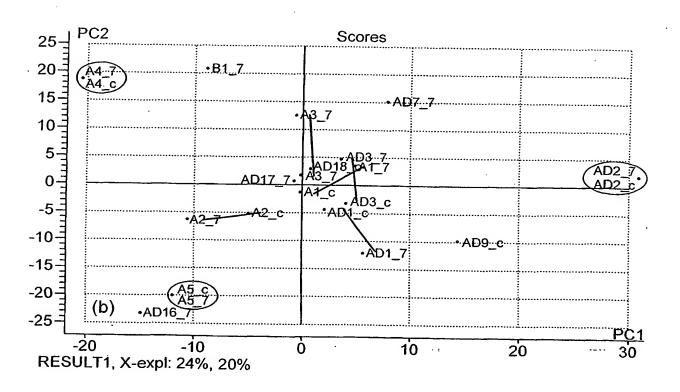
PCT/GB2003/005102

1/12

FIG. 1

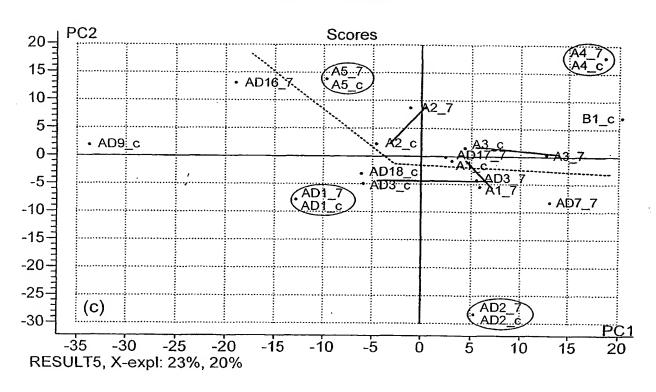
Effect of Direct Standardization (DS) on the Alzheimer Data measured in two different series of experiments

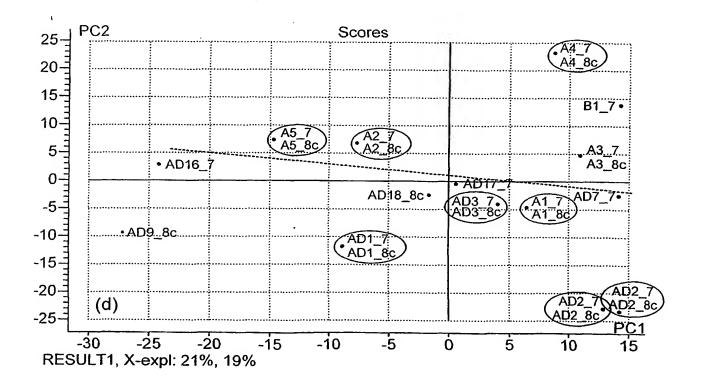


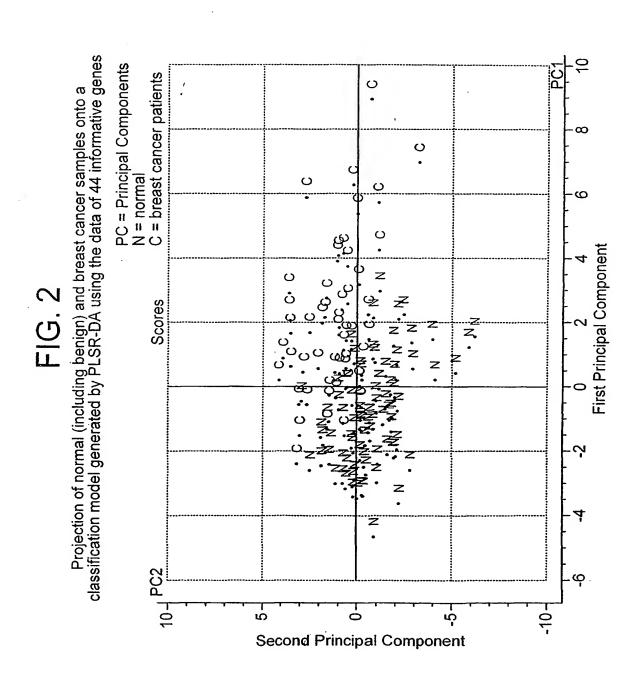


PCT/GB2003/005102

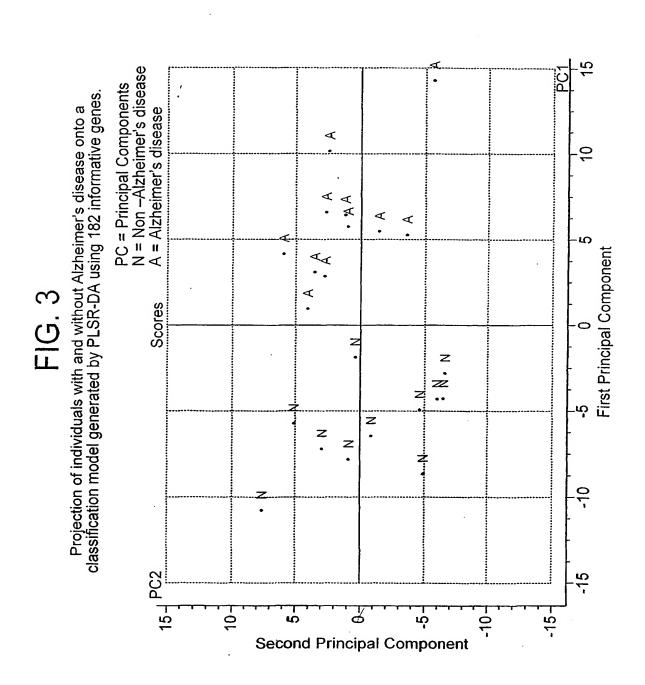
FIG. 1cont'D



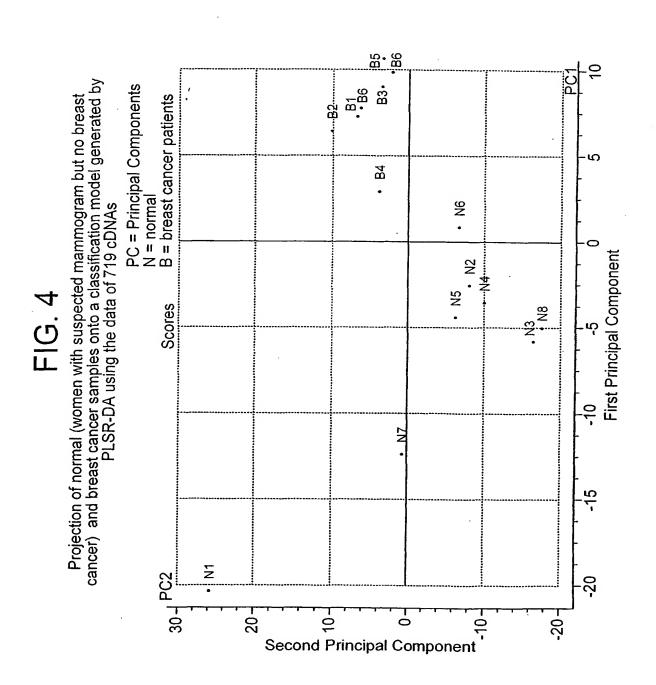




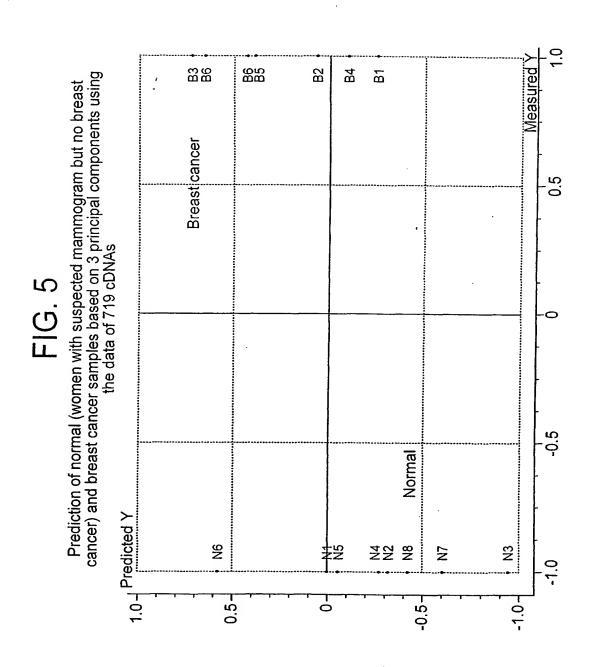
4/12

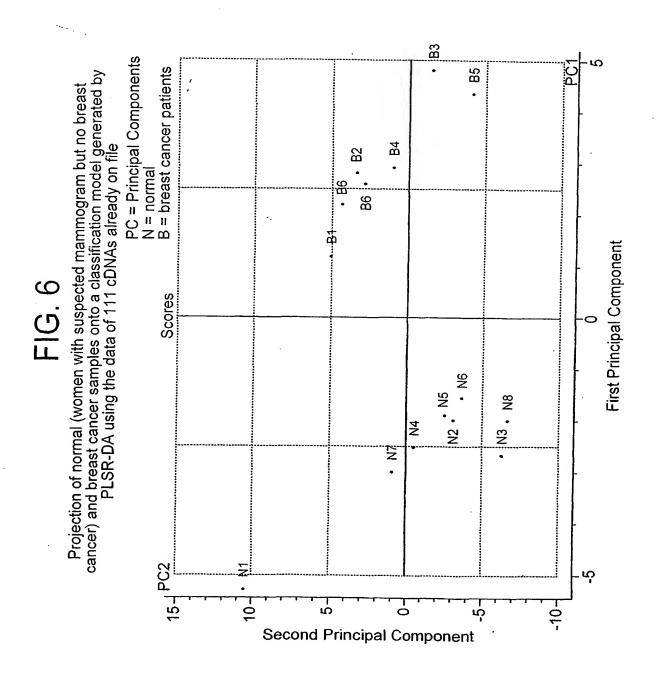


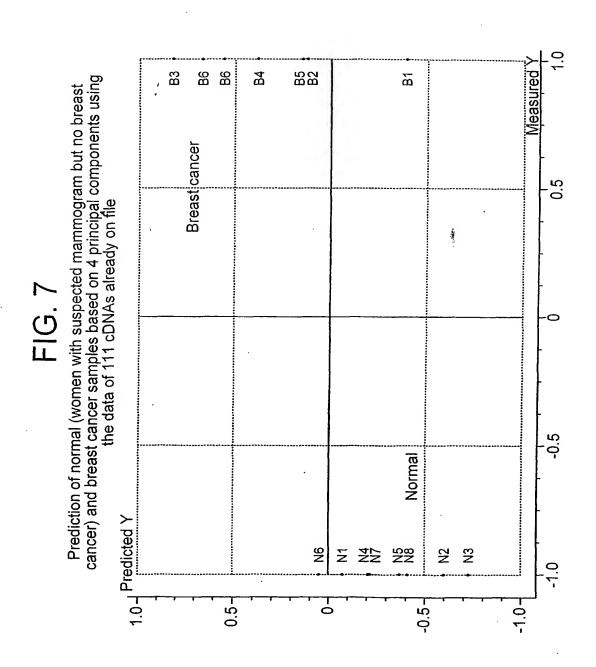
PCT/GB2003/005102

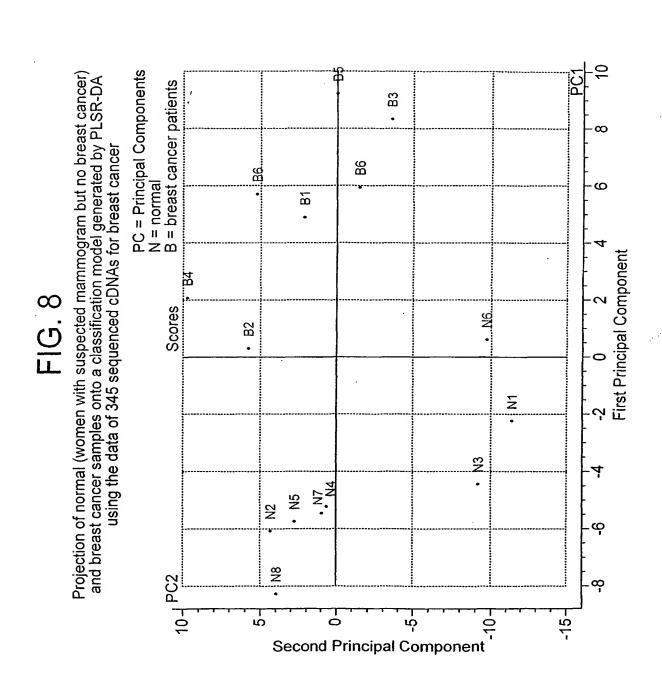


PCT/GB2003/005102

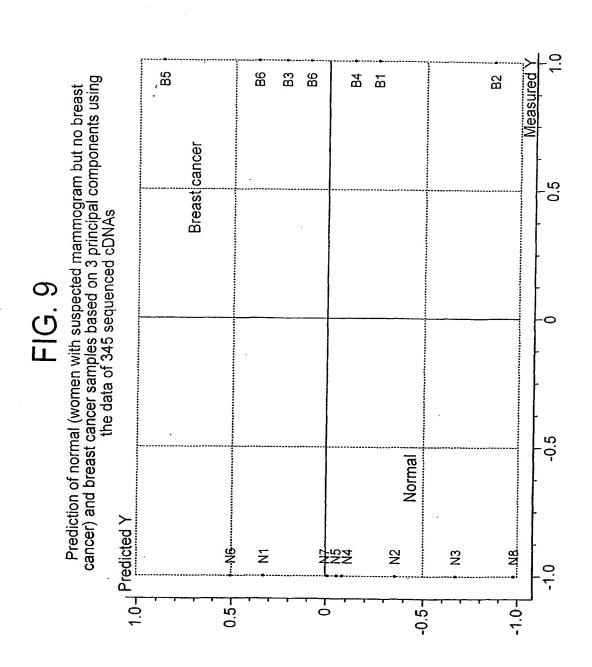


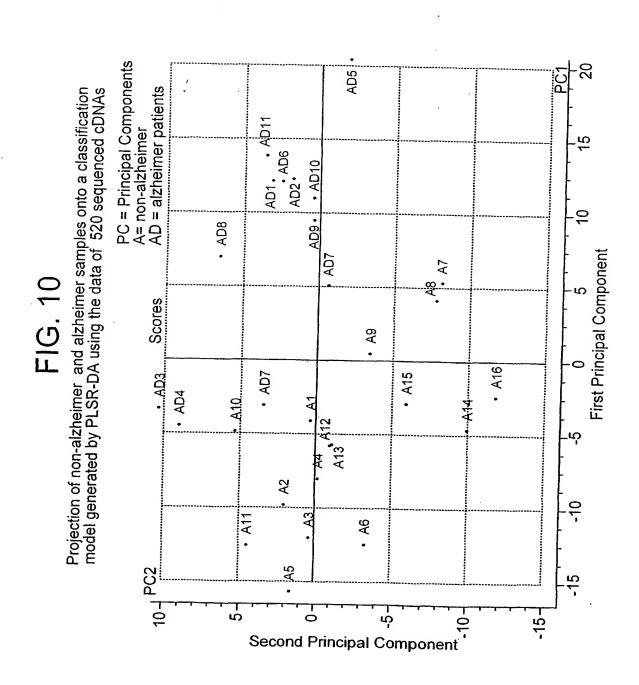






PCT/GB2003/005102





PCT/GB2003/005102

12 / 12

